FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF DOMPERIDONE FROM SELECTED SOLID DISPERSIONS - AN ATTEMPT TO IMPROVE *IN VITRO* DISSOLUTION, PATIENT COMPLIANCE AND MARKETABILITY

Dissertation work submitted to
THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI

In partial fulfillment of the award of degree of

MASTER OF PHARMACY

(Pharmaceutics)

Submitted by

C. ARTHER PAUL

Under the guidance of

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March 2009

COLLEGE OF PHARMACY

SRI RAMAKRISHNA INSTITUTE OF PARAMEDICAL SCIENCES

COIMBATORE – 641044

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Above all, I humbly submit my dissertation work, into the hands of **Almighty**, who is the source of all wisdom and knowledge for the successful completion of my thesis.

C.Arther Paul

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TAMILNADU PHARMACEUTICAL SCIENCES WELFARE TRUST

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Faculty of Pharmacy, PHARMACEUTICS Department, has been awarded scholarship of Rs. 2,000/- for securing THIRD rank in the M.Pharm project for the academic year 2008-09

SECRETARY

21-11-2008
Date

CHAIRMAN

Begin and close your day with prayer so that you may have a peaceful night free from dreams & nightmares.

To a good man, the whole world is good. Let us learn to treasure only good & reject the evil in everything.

Speak the truth & remain non-violent at any cost.

I am not against the wealth but the wealth that enslaves.

The real property a parent can transmit to all equally is his or her character & educational facilities. Have a clean companions-clean friends & clean books.

Seven social sins:

1. Politics without principles
2. Wealth without work
3. Pleasure without conscience
4. Knowledge without character
5. Commerce without morality
6. Science without humanity
7. Worship without sacrifice.

-Mahatma Gandhi

PURPOSE OF STUDY

Drug substances most frequently are administered orally by means of solid dosage forms such as tablets and capsules. In a number of cases it has been shown that the drug substance's solubility and other physiochemical characteristics have influenced its physiological availability from solid dosage forms[Edward M et al., 2005]. The chain of events that occur following administration of a solid dosage form such as a tablet or a capsule until its absorption into systemic circulation are depicted below.

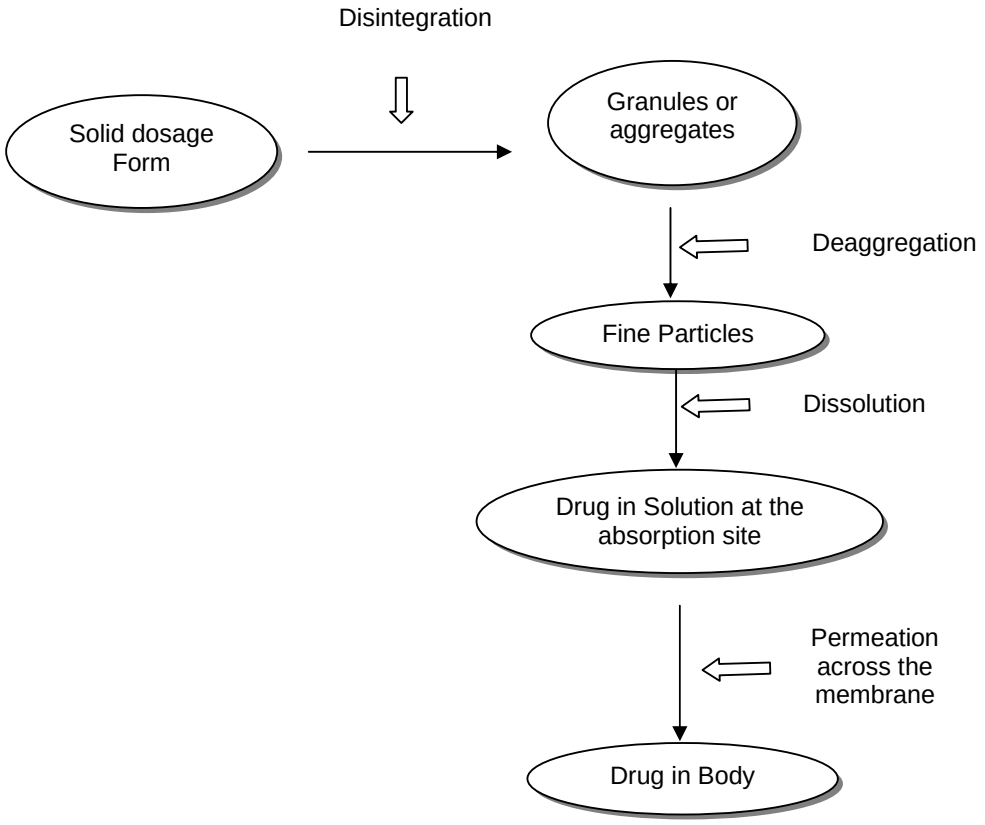


Figure 1: Schematic representation of steps involved in the absorption of solid dosage forms

Solid drugs administered orally for systemic activity must dissolve in the gastrointestinal fluids prior to their absorption. Thus, the rate of dissolution of drugs in gastrointestinal fluids could influence the rate and extent of their absorption. The rate of dissolution of a solid is a function of its solubility in the dissolution medium; the latter could influence absorption of the relatively insoluble drugs.

The rate of dissolution can be altered via physical intervention. When the absorption of a drug is dissolution rate limited a more soluble and faster dissolving form may be utilized to improve the rate and extent of bioavailability[Deodatt A et al., 1989].

The loss of drug on first passage through the liver once it is absorbed into the systemic circulation is called the hepatic first pass effect. Drugs with poor bioavailability due to hepatic first pass effect can be administred through buccal and sublingual route to enable presystemic absorption and to bypass hepatic first pass effect, thus ensure better bioavailability. Sublingual and Buccal tablets are therefore ideal for potent, low dose drugs which are undergoing metabolism through hepatic first pass effect[Salmon A. et al .,1989].

When bioavailability is very low ex: - < 20 %, inter and intra subject variability in bioavailability are magnified and incomplete oral bioavailability can become a great concern. If bioavailability average 20%, for example then 80% of a dose is wasted. So maximizing bioavailability contributes to increasing the cost effectiveness of the drug[Navnit H et al., 2008].

Several drugs have poor aqueous solubility to have a bearing on dissolution rate. The matter is of great concern when the solubility is less than 1-2 mg /ml in the pH range of 2-8.

It is estimated that 50% of the population have problems swallowing the tablets. This leads to poor or even noncompliance with the treatment and thus has a negative effect on the efficiency of the treatment[Seager.H 1998].

Domperidone a prokinetic D_2 receptor antagonist used in the treatment of nausea and vomiting as well as chemotherapy induced nausea and vomiting. It is practically insoluble in water and undergo extensive hepatic metabolism. According to the biopharmaceutical classification, it is a class II drug. The oral bioavailability of Domperidone is only 13 – 17 % due to poor aqueous solubility and hepatic first pass effect.

So the main objective of the present study aims

- To overcome the problem of poor bioavailability due poor aqueous solubility
- To overcome the problems of poor bioavailability due to hepatic first pass effect.
- To improve the palatability of the drug through formulation design.
- To improve the cost effectiveness of the drug.
- To draw a marketing strategy for the brand extension.

The research work envisaged was

1. Literature survey on solid dispersion methods and carriers for solid dispersion.
2. Preparation, characterization and evaluation of solid dispersions of Domperidone with PEG 4000, PEG 6000 and PEG 8000.
3. Formulation of non sugar muco adhesive sweetener (NSMAS).
4. Formulation and evaluation of Orodispersible tablets of Domperidone from selected solid dispersions of Domperidone.
5. Stability studies on formulation.

INTRODUCTION

When the drug is administered in a solid dosage form such as tablet, capsule, or suspension it must be released from the dosage form and dissolved in the gastrointestinal fluids before it can be absorbed. Considering the principle of drug absorption by a passive transport mechanism

$$Jw = Pw \times Cw$$

Where Jw – absorption rate

Pw – intestinal wall permeability

Cw – drug concentration at intestinal wall

Therefore maximum absorption rate is

$$Jw(max) = Pw \times solubility$$

As permeability being constant, the solubility as well as the rate of dissolution is the rate limiting step for the absorption[Wadke. D.A et al., 1989.]

The dissolution rate limited absorption corresponds with the increase in dose. The concept of dose number was introduced to further understand the dose limitation in the rate and extent of absorption.

$$\text{Dose number } D_o = \frac{Dose}{250\ X\ solubility}$$

(Note: 250 ml is considered as volume in the stomach)

Therefore a higher dose number which is generally associated with a high dose for a poorly soluble drug result in poor, incomplete, and variable absorption. Generally a dose number less than 10 is desired for higher absorption and bioavailability[Loben B.R and Amidon GL, 2000].

BIOPHARMACEUTICS CLASSIFICATION SYSTEM

The BCS is a scientific framework which is included in the FDA guidelines for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the in vitro dissolution characteristics of the drug product, the BCS has taken into account three major factors: solubility, intestinal permeability, and dissolution rate, all of which govern the rate and extent of oral drug absorption from immediate release solid dosage forms[Yu LX, et al, 2002].

The solubility classification of a drug in the BCS is based on the highest dose strength in an immediate release product. A drug substance is considered highly soluble when the highest strength is soluble in 250 ml or less of aqueous media over the pH range of 1.0 – 7.5; or else, the drug substance is considered poorly soluble. The volume estimate of 250 ml is derived from typical bio equivalence study protocols that prescribe administration of a drug product to human volunteers with a glass (about 8 ounces) of water.

The permeability classification is based directly on the extent of intestinal absorption of a drug substance in humans or indirectly on the measurement of the rate of mass transfer across human intestinal membrane. Animal or in vitro model capable of predicting the extent of intestinal absorption in humans may be used as alternative, e.g., in situ rat perfusion models and in vitro epithelial cell culture models. A drug substance is considered highly permeable when the extent of intestinal absorption is determined to be 90% or higher. Otherwise, the drug substance is considered to be poorly permeable.

An immediate release drug product is characterized as a rapid dissolution product when not less than 85% of the labeled amount of the drug substance dissolves within 30 minutes using USP Apparatus 1 at 100 rpm or USP Apparatus II at 50 rpm in a volume of 900 ml or less of each of the following media: (i) acidic media, such as 0.1 N HCl or USP simulated intestinal fluid without enzymes. (ii) A pH 4.5 buffer and (iii) a pH 6.8 buffer or USP simulated intestinal fluid without enzymes. Otherwise, the drug product is considered to be a slow dissolution product.

The BCS classifies drugs into four categories depending on their solubility.

Table 1: Biopharmaceutics classification system

Class	Solubility	Permeability
I	HIGH	HIGH
II	LOW	HIGH
III	HIGH	LOW
IV	LOW	LOW

Class I drugs are those which should have more than 90% absorption rate. Class II drugs are those with solubility too low to be consistent with the complete absorption, even though they are highly membrane permeable.

Class III is the mirror image of class II. These drugs have good solubility but were not capable of penetrating the gut wall quickly enough for the absorption to be complete. Class IV compounds have neither sufficient solubility nor permeability for absorption to be complete. Although they certainly do not possess optimal properties, some drugs in this category may still be absorbed well enough to permit oral administration.

Typically dissolution rate limited drugs are BCS II and IV compounds.

Formulation plays a major role in determining the rate and extent of absorption of drug candidate which has reasonable membrane permeability and the absorption is dissolution rate limited. When water solubility is 1 µg/ml which is often the case for contemporary drug candidates, the bioavailability from conventional tablet formulation may be unacceptable[Lipinski.C.2000].

The choice of formulation is often critical for establishing a successful product for oral administration of a class II drug. Various successful approach to formulate poor water soluble crystalline drugs into oral dosage forms include particle size reduction, formation of salts, complexes or co crystals, amorphous formulations, lipid based formulations, and prodrug approaches.

The dissolution rate of crystalline drug from a solid dosage form can be increased by reducing the particle size and increasing the surface area for dissolution. During the dissolution process, a solid dosage form, i.e., a tablet or capsule will undergo the process of wetting, disintegration, deagglomeration, dislodgement, and dissolution. The size of the contact surface is critical for all the reactions and mass transfer.

According to the modified Noyes-Whitney equation

$$\frac{dW}{dt} = \frac{DA(C_s - C)}{L}$$

where dW/dt is the rate of dissolution, “A” is the surface area available for dissolution, “D” is the diffusion coefficient of the compound, “Cs” is the solubility of the compound in the dissolution medium, “C” is the

concentration of drug in the medium at time t and “L” is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound[Noyes A.A and Whitney W.R, 1897, Nernst W, 1904].

Particle size reduction can increase the dissolution rate of a drug based on several aspects such as increased surface area, decreased diffusion layer, increased saturation solubility , and less sensitive to luminar hydrodynamics.

The bioavailability of a weak acid or weak base can be improved by the selection of an appropriate salt which is readily more soluble in the physiological fluids.

Co-crystal approach uses solvates, hydrates or eutectics to improve the solubility especially for non ionizable drugs. Careful selection of ligand or guest molecules can also increase solubility and or permeability.

Amorphous formulations include “solid dispersion and solid solutions” which can be formed using variety of technologies including solvent controlled precipitation, spray drying, hot melt extrusion, and fluid bed technology etc.

Prodrugs are also a common approach for improving the bioavailability.

SOLID DISPERSIONS

Solid dispersion is defined as the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or the melting-solvent method.

The dispersion of a drug or drugs in a solid diluent or diluents by traditional mechanical mixing is not included in this category. The term co-precipitate (more accurately) co-evaporate has also been frequently used when a solid dispersion is prepared by a solvent method.

ADVANTAGES OF SOLID DISPERSIONS

- Solid dispersion of drugs in solid state is helpful in stabilizing unstable drugs.
- The PEGs may protect certain drug e.g. cardiac glycosides against the decomposition by saliva and allow buccal absorption.
- Solid dispersions may be thermodynamically more active form of drug and directly influence the diffusion and release rate.
- An increased diffusion of steroid from the ointment was obtained.e.g. Solid dispersion of prednisolone urea dispersion.
- Solid dispersion technology can be used to solidify liquid drugs.e.g. Clofibrate and benzyl benzoate.

DISADVANTAGES OF SOLID DISPERSIONS

- Tackiness and decomposition during preparation and formulation.
- The oral administration of solid dispersions without concomitant reduction in dose may result in higher incidence of adverse effect. E.g. ulceration of indomethacin-PEG 6000 dispersion.
- Difficulty in pulverization of solid dispersion.
- Drug carrier incompatibility.
- Poor flow and mixing properties.
- Sifting of the solid dispersions, which are usually soft and tacky.

CLASSIFICATION OF SOLID DISPERSIONS

1. Simple eutectic mixtures

Solid eutectic mixtures are usually prepared by rapid cooling of a co-melt of two components in order to obtain a physical mixture of very fine crystals of the two components. When the preparation is dissolved in aqueous medium the carrier will dissolve rapidly, releasing very fine crystals of drug which offers large surface area thereby improvement in dissolution is effected[Sekiguchi.K and Obi.N, 1961., Goldberg.A.H, et al., 1966].

2. Solid solutions

Solid solutions of a poor water soluble drug dissolved in a carrier with relatively good aqueous solubility are of particular interest as a means of improving oral bioavailability. In the case of solid solutions, the drug's particle size has been reduced to its absolute minimum viz. the molecular dimensions and the dissolution rate are determined by the dissolution rate of the carrier. By judicious selection of a carrier, the dissolution rate of the drug can be increased by up to several orders of magnitude. Solid solutions can be classified according to two methods. First, they can be classified according to their miscibility (continuous versus discontinuous solid solutions) or second, according to the way in which the solvate molecules are distributed in the solvendum (substitutional, interstitial or amorphous)[Goldberg.A.H et al., 1965].

2.2.1. CONTINUOUS AND DISCONTINUOUS SOLID SOLUTIONS

2.2.1.1. Continuous solid solutions

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical literature to date.

2.2.1.2. Discontinuous solid solutions

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited.

2.2.2. Substitutional crystalline, interstitial crystalline and amorphous solid solutions

2.2.2.1. Substitutional crystalline solid solutions

Classical solid solutions have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules[Hume.R.W and Raynor.G.V, 1954].

2.2.2.2. Interstitial crystalline solid solutions

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter[Reed-Hill R.E, 1964]. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

2.2.2.3. Amorphous solid solutions

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using griseofulvin in citric acid, Chiou and Riegelman were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers that were used in early studies included urea and sugars

such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose[Chiou W.L and Riegelman.S, 1969].

SOLID DISPERSION TECHNIQUES

1. Melting or Fusion Method

The melting or fusion method was first proposed by Sekiguchi and Obi to prepare fast release solid dispersion dosage forms[Sekiguchi. K and Obi N, 1961]. In this method the physical mixture of drug and the water soluble carrier is heated directly until it is melted. The melted mixture is then cooled and solidified in an ice bath under vigorous stirring. The final mass was crushed, pulverized and sieved. The dispersion can also be cooled through the process of spray congealing using spray drying equipment. The melted material is sprayed onto cold metal surfaces, which forms pellet of the dispersion. This does not require grinding and therefore no alteration of the crystal modification of the drug occurs. E.g. solid dispersion of sulphamethoxazole, acetaminophen, chloramphenicol, tolazamide, steroids.

Advantages

- Simplicity and economy.
- This method also advantageous for compounds, which do not undergo significant thermal degradation
- Super saturation of a solute or drug in a system can often be obtained by quenching of the melt rapidly from high temperature.

Disadvantages

- The main disadvantage of the melt method includes thermal degradation, sublimation and polymeric transformation, which can

affect the physicochemical properties of the drug including its rate of dissolution.

- The temperature at which the dispersion solidifies affects crystallization rate and may alter both the size of the crystal and hardness of the dispersion. This may result in tacky or glassy and unmanageable dispersions, which will require storage at elevated temperature to facilitate hardening.

2. Solvent Evaporation Method

This method involves dissolving the drug and carrier in a suitable organic solvent followed by evaporation of the solvent to form solid dispersion involves dissolving the drug and carrier in a suitable organic solvent followed by evaporation of the solvent to form solid dispersion. The mass was then stored in dessicator, pulverized and sieved. Removal is accomplished by various means. The most common approach is the application of reduced pressure at a fixed temperature to evaporate the organic solvent. Temperatures of 125^0C for 25 minutes, 115^0C for one hour[Chiou .W.I and Riegelman.S 1970], -5^0c and reduced pressure followed by drying for 12 hours in vacuum have been used [Malone, M.H,et al.,1966].

Spray drying is another approach by which solvent removal can be accomplished and it is probably the fastest way of removing solvent [Bloch, D.W, et al., 1983]. The freeze drying technique is also employed to prepare solid dispersions by removal of aqueous solutions[Sekikawa.H, et al., 1983]. E.g. solid dispersion of β-carotene-PVP, griseofulvin-PVP and reserpine-deoxy cholic acid.

Advantages

- The procedure is suitable for drugs that are thermo labile.
- The thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of the organic solvents.
- For aqueous system, frozen temperature can be used to evaporate the solvent, which can enhance the integrity of the drug.

Disadvantages

- Difficulty in complete removal of solvent.
- Finding a suitable solvent that will dissolve both the drug and carrier is very difficult.
- Plasticization of some polymers such as poly vinyl pyrrolidone has occurred with the use of some solvents.
- It is important that the rate of evaporation of a solvent is controlled so as to control the particle size of the drug. This in turn will affect the rate of dissolution of the drug in the solid dispersion.

3. Fusion-Solvent Method

In the fusion solvent method, a carrier(s) is/are melted and the drug(s) is/are incorporated in the form of a solution. If the carrier is capable of holding a certain proportion of liquid yet maintaining its solid properties, and if the liquid is innocuous, the need for removal is eliminated. This method is particularly useful for drugs that have high melting points are that are thermo labile. The feasibility of the method has been demonstrated for spironolactone and griseofulvin dispersions in polyethylene glycol 6000 (PEG 6000)[Chiou. W.I and Riegelman. S, 1971] . E.g. solid dispersion of clofibrate, methyl salicylate, benzyl benzoate.

MECHANISM OF INCREASED DISSOLUTION RATE BY SOLID DISPERSION SYSTEM

- In the case of glass solutions, and amorphous dispersions, particle size is reduced to a minimum level. This can result in an enhanced dissolution rate due to both an increase in surface area and solubilization.
- The carrier material as it dissolves may have a solubilization effect on the drug.
- The carrier material may also have an enhancing effect on the wettability and dispersibility of the drug in the dissolution medium. Then should retard any agglomeration or aggregation of the particles, which can slow the dissolution process.
- Formation of metastable dispersion that has a greater solubility would result in faster dissolution rates.

CARRIERS USED FOR SOLID DISPERSION SYSTEMS[Christian.L and Jennifer.D, 2000]

1. Polyethylene glycols (PEGs)
2. Polyvinylpyrrolidone (PVP)
3. Polyvinyl groups
   - Polyvinyl alcohol (PVA)
   - Crospovidone
   - Polyvinylpyrollidone-polyvinylacetate copolymer (PVP-PVA)
4. Cellulose derivatives
   - Hydroxypropylmethylcellulose (HPMC)
   - Hydroxypropylcellulose (HPC)
   - Carboxymethylethylcellulose (CMEC)
   - Hydroxypropylmethylcellulose phthalate (HPMCP)

5. Polyacrylates and polymethacrylates
   - Eudragit E
   - Eudragit L
6. Urea
7. Sugar, polyols and their polymers
   - Dextrose
   - Sucrose
8. Emulsifiers
   - Sodium Lauryl Sulphate
   - Tween 80
9. Organic acids and their derivatives
   - Succinic acid
   - Citric acid
10. Other carriers
    - Phospholipid
    - Pentaerythritol

Table 2: Solid dispersion of therapeutic agents

Drug	Carriers	Method	Type of solid dispersion	Effect of dissolution rate
Allopurinol	PVP	S	Not studied	Increased
Benzybenzoate	PEG 6000	MS	Not studied	Increased
Chloramphenicol	Urea	M	Solid solution	Increased
Clofibrate	PEG 6000	MS	Not studied	Increased
Corticosteroids	Sugars	M	Not studied	Increased
Diazepam	PEG 4000	M	solid solution	Not studied
Griseofulvin	Succinic Acid	M	Solid solution	Increased

	PVP	S	Not studied	Increased
	PEG-4000	MS	Not studied	Increased
	PEG-6000	M,S	Not studied	Increased
	PEG 2000	M	Not studied	Increased
	Citricacid	M	Glass suspension	Increased
Indomethacin	PEG 6000	M	Not studied	Increased
Methylsalicylate	PEG 6000	S	Not studied	Increased
Paracetamol	Urea	M	Solid solution	Increased
Mannitol	M	Eutetic	Increased	
Primidone	Citric acid	M	Glass solution	Increased
Reserpine	PVP	S	Not studied	Increased
Sulfathiazole	Urea	M	Simple eutectic	Not studied
Tobultamide	PEG-4000	S	Not studied	Increased
	PEG-6000	S	Not studied	Increased
	PEG4000	M,S	Not studied	Increased
	PEG-2000	M,S	Mono acetic	Not studied
	PVP	S	Not studied	Increased
	PEG-8000	M,S	Not studied	Increased
	PVP	S	Not studied	Increased
	PEG-6000	S	Not studied	Increased
	PEG-4000	M	Not studied	Increased

o *M-Melting Method S- Solvent Method MS- Melting solvent method

ORODISPERSIBLE TABLETS

Orodispersible tablets (ODTs) are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed without the aid of additional water. These tablets disintegrate within 3 minutes[European pharmacopoeia 1996]. Orodispersible tablets are otherwise known as Orally Disintegrating Tablets, Rapidly Disintegrating Tablets and Fast Dissolving Tablets.

For a tablet to be classified as an ODT tablet the disintegration time should be sufficiently rapid for the patient to not feel the need or compulsion to chew. One of the greatest benefits of ODTs over conventional tablets is enhanced patient compliance and acceptance related to both feasibility and convenience of dosage administration[Cheu P et al., 2004]. As many as 50 % of the population have difficulty swallowing intact tablets and hard gelatin capsules[Seager.H, 1998].These include pediatric and geriatric populations who have difficulty in swallowing large tablets.

Patients who are bedridden, mentally retarded, uncooperative, nauseous, and those suffering from nervous or anatomical disorders of the larynx or esophagus, or on reduced liquid intake diets also cannot swallow conventional tablets[Shen Y et al., 2007].

The bioavailability between the Orodispersible tablets and conventional tablets differ considerably. With conventional tablets the contact time between the drug substance and Oromucosal tissues are minimal and most of the absorption takes place in the stomach and or the intestines. However, drug released from ODTs also has the opportunity to be absorbed by local Oromucosal tissues and Pregastric regions, especially if the residence time in the mouth is prolonged. Oromucosal and pregastric absorption can potentially produce a rapid response, and partial

avoidane of first pass effects and gastrointestinal irritation **Freudenreich.O, 2003.** It is apparent that the formulation of orally disintegrating tablets can significantly change the bioavailability of some drugs.

Advantages of ODT

- Best for patients with esophageal problems and have difficulties of deglutition tablets.
- High drug loading is possible
- Leave minimum residue in the mouth after oral administration
- Guarantee a rapid onset of action when required
- Patient compliance due to pleasant mouth feel
- Cost effective**Kundu.S and Sahoo.P.K, 2008**.

Disadvantages of ODT

- ODTs may not be beneficial for those who with very dry mouth.
- Masking the bitter tasting drugs post formidable challenges in formulating as ODTs.
- It is difficult to achieve sufficient strength of ODTs to withstand the rigors of the manufacturing process and handling.
- Coatings of active pharmaceutical ingredients are often needed for taste masking of bitter drugs**Kundu.S and Sahoo.P.K, 2008**.

Technologies for manufacturing ODTs

Technologies for manufacturing ODTs include the freeze drying method, cotton candy technology, and compressed tablets. The Zydis® (R.P.Scherer, Troy,Michigan,U.S.A) technology is used to make freeze dried wafers which dissolve nearly instantly in the mouth and leave no gritty residue. Compressed tablets usually dissolve slower than the freeze dried wafers and may leave a gritty mouth feel if insoluble excipients are used. However the compressed tablets technology is less expensive and may be more suited for loading large amount of active ingrdients.

1. Freeze drying technology

Freeze drying or lyophilization technology was introduced by Zydis delivery system developed by R.P.Scherer. It is a mixture of gelatin, sugar(s), active ingredients, and other components poured into the depression of a blister pack. Water is sublimed away during lyophilization leaving a highly porous, relatively soft sold. The resulting wafers dissolve or disperse on the tongue rapidly in about three to five seconds. Some of the limitations of the freeze dried wafers are drug solubility and a drug loading limitation of about 60 mg for water soluble drugs[Seager H, 1998].The wafers are also moisture sensitive and very fragile, requiring special packaging.

2. Cotton candy technology

Cotton candy process also known as the candy-floss process, which involves centrifugation to produce floss like crystalline structure. In this technology, the matrix is formed from saccharides or polysaccharides processed into an amorphous floss through a shear foam process. The matrix is crushed and milled to make a flow able, compactable, and highly soluble filler. Because of the formation of porous three dimensional structures with the active ingredients encased in the pores, the resulting surface area is high. Therefore, dispersion and dissolution occur quickly when the product is placed in the mouth[Yoo.J, et al., 1998].

3. Tablet compression technology

ODTs can be formed by either direct compression, wet granulation or by a wet compression method. In the wet compression method, water is added to a power blend and the mixture is kneaded until a homogenous wet power mass is formed. The mass is then extruded through a sieve. Wet granules are then compressed into tablets. The wet compression method may not be suitable for active materials that are physically or chemically unstable in the presence of water.

The direct or dry compression method is generally preferred because it is simpler, easier to automate, and avoids direct contact of water with the active material. As with wet compression, it is often capable of producing ODTs with sufficient physical robustness to allow physical handling and packaging[Rowe.R and Roberts.R, 1998].

4. Moulding

Moulding is done by two methods compression moulding and heat moulding. Compression moulding tablets are prepared compressing a powered mixture previously moistened with solvent (usually ethanol or water) into mould plates to form a wetted mass. In heat moulding the drug is dissolved or dispersed in a molten matrix. Now vacuum lyophilization is a new technique in which evaporation of solvent from a drug solution or suspension is done at standard pressure. Tablets produced by moulding are solid dispersions, having advantage of very rapid dissolution (5 to 15 sec) and can load high dose. The major disadvantages are high cost of production, weak mechanical strength and possible limitation in stability[Dobetti.L ,2001].

Superdisintegrants

Disintegrants are very important component of compressed ODTs because they often are primarily responsible for the fast disintegration in the mouth. ODTs can contain either superdisintegant or an effervescent system as a disintegrating agent. An effervescent system (e.g., sodium bicarbonate and citric acid combination) generally provides a highly effective disintegrating system. The release of carbon dioxide when the effervescent agents come in contact with water helps to collapse the tablet matrix. To minimize any possible unpleasantness owing to a fizzing sensation in the mouth, formulators may choose to minimize the level of effervescent ingredients used in the formulation.

In conventional tablets super disintegrants, such as croscarmellose sodium, sodium starch glycolate, and crospovidone are generally effective at lower concentrations than the traditional disintegrant, starch, and may be used at 2-5%. Although high levels of superdisintegrants do not necessarily produce faster disintegration in conventional tablets, as much as 15% of superdisintegrants may be beneficial in ODTs.

Superdisintegrants are strongly hygroscopic materials that aid in wicking water from the saliva into the internal structure of the tablets. An advantage of using superdisintegrants over the effervescent system is that they are less vulnerable than the latter to the detrimental effect of moisture. Nevertheless, the hygroscopicity of superdisintegrant is such that both their functionality and tablet stability can be compromised by excessive exposure to high humidity. Of the three widely used superdisintegrants, croscarmellose sodium seems to be less affected by high moisture level in regards to functionality,but all disintegrants are vulnerable to the detrimental effect of humidity.

High levels of disintegrants ,high level of soluble fillers, heat generated from the tablet presses, and atmospheric moisture can easily induce or promote stickiness at the punches which may pose a challenge to the formulation scientist[Hahm HA 2002].

VOMITING

Vomiting is a complex process that consists of a pre-ejection phase (gastric relaxation and retroperistalsis), retching (rhythmic action of respiratory muscles preceding vomiting and consisting of contraction of abdominal and intercostal muscles and diaphragm against a closed glottis), and ejection (intense contraction of the abdominal muscles and relaxation of the upper esophageal sphincter). This is accompanied by multiple autonomic phenomena including salivation, shivering, and vasomotor changes. During prolonged episodes, marked behavioral changes including lethargy, depression, and withdrawal may occur.

The process appears to be coordinated by a central emesis center in the lateral reticular formation of the mid-brainstem adjacent to both the chemoreceptor trigger zone (CTZ) in the area postrema (AP) at the bottom of the fourth ventricle and the solitary tract nucleus (STN) of the vagus nerve. The lack of a blood-brain barrier allows the CTZ to monitor blood and cerebrospinal fluid constantly for toxic substances and to relay information to the emesis center to trigger nausea and vomiting. The emesis center also receives information from the gut, principally by the vagus nerve (*via* the STN) but also by splanchnic afferents *via* the spinal cord.

Two other important inputs to the emesis center come from the cerebral cortex (particularly in anticipatory nausea or vomiting) and the vestibular apparatus (in motion sickness). In turn, the center sends out efferents to the nuclei responsible for respiratory, salivary, and vasomotor activity, as well as to striated and smooth muscle involved in the act of vomiting. The CTZ has high concentrations of receptors for serotonin (5-HT_3), dopamine (D_2), and opioids, while the STN is rich in receptors for enkephalin, histamine, and ACh, and also contains 5-HT_3 receptors. A

variety of these neurotransmitters are involved in nausea and vomiting and an understanding of their nature has allowed a rational approach to the pharmacological treatment of nausea and vomiting[Pankaj.J.P.2006].

CYTOTOXIC INDUCED NAUSEA AND VOMITING (CINV)

Nausea and vomiting are well recognized in many diverse clinical situations, suggesting that no single mechanism is likely to be responsible for their production. Cytotoxic drugs used in the treatment of a range of malignancies, may produce severe gastrointestinal toxicity. This may lead to a refusal of curative therapy or to a decline in palliative benefits offered by cytotoxic treatment. The exact mechanism of chemotherapy induced nausea and emesis are poorly understood; however, an appreciation of the vomiting process remains essential to a rational approach to the therapeutics of anti-emesis. Chemotherapy induced vomiting is thought to act via the CTZ/AP. Despite the identification of several important neurotransmitters, no single anti-emetic agents have been able to counteract chemotherapy induced emesis with universal success. This suggests that complex patterns of chemoreception and neurotransmission are occurring within the AP-tractus solitaries-vomiting centre axis.

The most commonly used anti-emetics are those which block dopamine, histamine or acetylcholine receptors and selective receptor antagonism has formed the basis of the approach to anti-emetic therapeutics[Edwards C M,1988].

Domperidone is a benzimidazole derivative which is a peripheral dopamine receptor blocker promoting gastric motility. It is thought to offer advantages over conventional anti-emetics since it does not cross the blood brain barrier and therefore produce a low incidence of CNS side

effects including sedation and extrapyramidal reactions. Domperidone, like metoclopramide also acts at the CTZ,D_2 blockade. Domperidone has been shown to be superior to placebo and either superior or equivalent to metoclopramide [Harris Al, and cantwell, 1984].

ANTIEMETICS CLASSIFICATION

Antiemetics generally are classified according to the predominant receptor on which they are proposed to act [Edwards C M, 1988, Rang H.P., et al, 2003].

1. Anti cholinergics
   - Hyoscine
   - Dicylomine
2. H_1 antagonists
   - Promethazine
   - Diphenhydramine
   - Dimenhydrinate
   - Cyclizine
   - Meclizine
   - Cinnarizine
3. Dopamine receptor antagonists
   - Chlorpromazine
   - Prochlorperazine
   - Trifluoperazine
   - Thiethylperazine
   - Haloperidol
   - Droperidol
4. Prokinetic drugs
   - Metaclopramide
   - Domperidone
   - Cisapride
   - Mosapride
5. $5HT_3$ antagonist

Ondansetron
Granisetron
Tropisetron
Dolasetron
Palonosetron

6. Adjuvant antiemetics

a) Glucocorticoids
   - Dexamethasone
   - Methylprednisolone

b) Benzodiazepines
   - Lorazepam
   - Alprazolam

c) Cannbinoids
   - Dronabinol
   - Nabilone

d) NSAID's

e) Substance "p" receptor antagonist
   - Cisplatin

f) Other agents
   - Benzoquimanide
   - Trimethobenzamide
   - Alizapride

DRUG PROFILE

DOMPERIDONE

Domperidone is a D_2 receptor antagonist that acts in the CTZ. It has a peripheral prokinetic action to increase the motility of the esophagus, stomach and intestine. Domperidone does not penetrate the blood brain barrier to any extent and, it is free from central side effects[BP 1996].

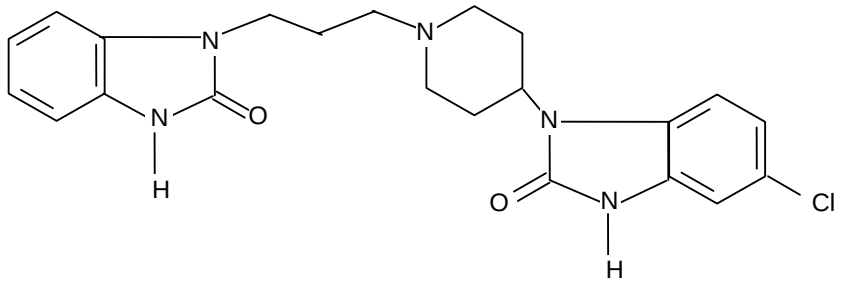
Chemical name

6-chloro-3-[1-[3-(2-oxo-3H-benzimidazol-1-yl) propyl] piperidin-4-yl]-1H-benzimidazol-2-one

Empirical formula

$C_{22}H_{24}ClN_5O_2$

Chemical Structure



Characteristics

White or almost white powder. Practically insoluble in water, soluble in dimethylformamide, slightly soluble in alcohol and in methanol. Melting point is 244°-248°C.

Pharmacology

Domperidone has peripheral dopamine receptor blocking properties, it increases esophageal peristalsis and increases lower esophageal sphincter pressure, increases gastric motility and peristalsis, and enhances gastro duodenal coordination, therefore facilitating gastric emptying and decreasing small bowel transit time.

Pharmacokinetics

Oral bioavailability 13-17 %

Protein binding 91- 93%

Onset of action 30 min -60 min

C_{max} - 90 min

Metabolism-hepatic via N-dealkylation(CYP3A4) and hydroxylation.

Half life elimination: 7- 9 hours

Excretion: feces (66%): urine (31%). www.drugbank .ca

Indications

Symptomatic management of upper gastro intestinal motility disorders associated with chronic and sub acute gastritis and diabetic gastroparesis; prevention of GI symptoms associated with use of dopamine agonist anti-Parkinson agents. Domperidone is also used in chemotherapy induced nausea and vomiting[Edwards C M, 1988].

Pregnancy implications

Animal studies have not shown drug related teratogenic or primary embryo toxic effects on animal fetuses; however comparative studies have not been done in humans. Use only when benefit outweighs potential risk in a pregnant woman.

Lactation

Enters breast milk, not recommended.

Contraindications

Hypersensitivity to Domperidone or any component of the formulation; patients with gastro intestinal hemorrhage, mechanical obstruction, or perforation; patients with prolactin releasing pituitary tumor.

Drug interactions

Cytochrome P_{450} effect: substrate of CYP3A4 (minor)

Increased effect/toxicity: Domperidone may increase the rate of absorption of drugs from the stomach, absorption of sustained release or enteric coated tablets may be altered. QTc prolonging drugs should be used with caution in combination with Domperidone, includes type Ia and type III anti arrhythmics, some fluoroquinolones and selected antipsychotics (thioridazine,mesoridazine) .

Decreased effect: anticholinergics decrease the effect of Domperidone. Domperidone may slow the rate of absorption of drugs from the gastrointestinal tract (sustained release or enteric coated formulations).

Adverse drug reactions

Adverse drug reactions ranges between 1% and 10 %.

Central nervous system:

Head ache/ migraine (1%); does not cross blood brain barrier; fewer CNS effects compared to metoclopramide.

Gastrointestinal: xerostomia (2%)

Less than 1% ; dizziness, dysuria, edema, extra pyramidal symptoms(EPS), rarely galactorrhea, gynecomastia, hot flashes, increased serum prolactin, insomnia, irritability, nervousness, mastalgia, menstrual irregularities, pruritus, rash.

Dose and Administration

Adults

GI motility disorders: 10 mg 3 – 4 times/day, 15 – 20 minutes before meals;

Severe resistant cases 20 mg 3-4 tomes/day, 15 – 30 minutes before meals.

Maximum 80 mg/day.

Nausea/vomiting: 20 mg 3 – 4 times/day

Dosage adjustment in renal impairment: decrease dose to 10 – 20 mg 1 – 2 times/day.

Children:

Less than 2 yr and less than 35 kg: 10 – 20 mg 3- 4 times /day.

Stability

Store at room temperature of 15^{o} c to 30^{o} c (59^{o} F to 86^{o}F); protect from light and moisture.

Warnings/precautions

Domperidone may increase prolactin levels (dose dependent response). Elevated prolactin may be asymptomatic(clinical consequence of chronically elevated prolactin is unknown) or may present symptomatically as galactorrhea, gynecomastia, amonorrhea, or impotence (reversible upon decreasing dose or discontinuing drug).

QTc prolongation , life threatening tachy arrhythmias, and cardiac arrest have been reported after Domperidone use; there adverse effects may be precipitated in hypokalemic patients. Use with caution in patients with hepatic impairement.

Use caution when administering Domperidone to patients with a personal or family history of breast cancer, use with caution in patients on MAO inhibitors.

Safety and efficacy have not been established in pediatric patients.

Over dose / toxicology

Symptoms of over dose include CNS effects such as drowsiness, disorientation, and extra pyramidal reaction. And cardiovascular effects such as arrhythmias and hypertension.

Treatment is supportive. Extrapyramidal effects may be controlled by anticholinergic agents (benztropine 1- 2 mg I.M/I.V) or antihistaminics with high anticholinergic activity (diphenhydramine 25- 50 mg I.M/I.V)

Interaction with food

Delayed absorption but higher bioavailability due to reduced first pass metabolism in gut wall.

Additional information

The FDA has issued a warning concerning the off label use of Domperidone to increase milk production in breast feeding woman. Domperidone is not available for any use in the United States and does not have approval for this indication in other countries. However, the FDA is aware that woman is obtaining Domperidone from U.S compounding pharmacies and foreign sources for this purpose. The FDA note that there is health risks associated with the use of this product that is why it has been removed from marketing[Goodman and Gilman's, 2001].

POLYMER PROFILE

Polyethylene Glycol [Raymond C R, 2003]

1. Non proprietary names

BP : Macrogols

JP : Macrogol 4000
Macrogol 6000
Macrogol 8000

PhEur : Macrogola

USP/NF: Polyethylene glycol

2. Synonyms

Carbowax; carbowax sentry; lipoxol; lutrol E; PEG; Pluriol E; Polyoxyethylene glycol.

3. Chemical name

α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl)

4. Empirical formula

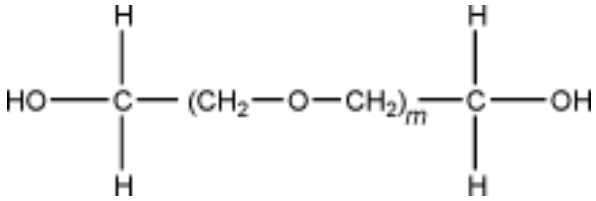
$HOCH_2(CH_2OCH_2)_mCH_2OH$ where *m* represents the average number of Oxyethylene groups.

The average molecular weights of polyethylene glycols are as follows. Note that the number that follows PEG indicates the average molecular weight of the polymer.

Molecular weight of polyethylene glycol polymers.

Grade	Average molecular weight
PEG 4000	3000–4800
PEG 4600	4400–4800
PEG 8000	7000–9000

5. Structural formula:



6. Functional category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

7. Description

The USP/NF 23 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures.

Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.

Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.

8. Typical properties

Density

- 1.11–1.14 g/cm^3 at 25°C for liquid PEGs;
- 1.15–1.21 g/cm^3 at 25°C for solid PEGs.

Melting point

- 50–58°C for PEG 4000;
- 55–63°C for PEG 6000;
- 60–63°C for PEG 8000;

Moisture content

Liquid polyethylene glycols are very hygroscopic, although hygroscopicity decreases with increasing molecular weight. Solid grades e.g. PEG 4000 and above, are not hygroscopic.

Surface tension

Approximately 44 mN/m (44 dynes/cm) for liquid polyethylene glycols; approximately 55 mN/m (55 dynes/cm) for 10% w/v aqueous solution of solid polyethylene glycol.

Viscosity (kinematic)

Specifications from PhEur 2005

Type of PEG	Density (g/cm^3)	Freezing point (°C)	Hydroxyl value	Viscosity (dynamic) [mPa s (cP)]	Viscosity (kinematic) [mm^2/s (cSt)]
4000	1.080	53–59	25–32	110–170	102–158
6000	1.080	55–61	16–22	200–270	185–250
8000	1.080	55–62	12–16	260–510	240–472

Viscosity of selected polyethylene glycols at 25°C and 99°C.

Type of PEG	Viscosity [mm^2/s (cSt)]	
	25°C	99°C
PEG 4000 solid	180	—
PEG 6000 solid	580	—
PEG 20000 solid	6 900	—

8. Solubility

All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher-molecular-weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

9. Stability and storage conditions

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid.

Polyethylene glycols and aqueous polyethylene glycol solutions can be sterilized by autoclaving, filtration, or gamma irradiation. Sterilization of solid grades by dry heat at 150°C for 1 hour may induce oxidation, darkening, and the formation of acidic degradation products. Ideally, sterilization should be carried out in an inert atmosphere. Oxidation of

polyethylene glycols may also be inhibited by the inclusion of a suitable antioxidant.

If heated tanks are used to maintain normally solid polyethylene glycols in a molten state, care must be taken to avoid contamination with iron, which can lead to discoloration. The temperature must be kept to the minimum necessary to ensure fluidity; oxidation may occur if polyethylene glycols are exposed for long periods to temperatures exceeding 50°C. However, storage under nitrogen reduces the possibility of oxidation.

Polyethylene glycols should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.

10. Safety

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials.

Adverse reactions to polyethylene glycols have been reported, the greatest toxicity being with glycols of low molecular weight. However, the toxicity of glycols is relatively low.

Polyethylene glycols administered topically may cause stinging, especially when applied to mucous membranes. Hypersensitivity reactions to polyethylene glycols applied topically have also been reported, including urticaria and delayed allergic reactions.

The most serious adverse effects associated with polyethylene glycols are hyperosmolarity, metabolic acidosis, and renal failure following the topical use of polyethylene glycols in burn patients. Topical

preparations containing polyethylene glycols should therefore be used cautiously in patients with renal failure, extensive burns, or open wounds. Oral administration of large quantities of polyethylene glycols can have a laxative effect. Therapeutically, up to 4 L of an aqueous mixture of electrolytes and high-molecular-weight polyethylene glycol is consumed by patients undergoing bowel cleansing.

Liquid polyethylene glycols may be absorbed when taken orally, but the higher-molecular-weight polyethylene glycols are not significantly absorbed from the gastrointestinal tract. Absorbed polyethylene glycol is excreted largely unchanged in the urine, although polyethylene glycols of low molecular weight may be partially metabolized.

The WHO has set an estimated acceptable daily intake of polyethylene glycols at up to 10 mg/kg body-weight.

In parenteral products, the maximum recommended concentration of PEG 300 is approximately 30% v/v as hemolytic effects have been observed at concentrations greater than about 40% v/v.

11. Application in pharmaceutical formulation or technology

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations. It has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.

Polyethylene glycols are used as ointment bases to the skin as they do not readily penetrate the skin, nonirritant and are water soluble. Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades.

Mixtures of polyethylene glycols can be used as suppository bases, for which they have many advantages over fats.

Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers. Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules.In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.

In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules. However, they have only limited binding action when used alone, and can prolong disintegration if present in concentrations greater than 5% w/w. When used for thermoplastic granulations, a mixture of the powdered constituents with 10–15% w/w PEG 6000 is heated to 70–75°C. The mass becomes pastelike and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required.

Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol. Animal studies have also been performed using polyethylene glycols as solvents for steroids in osmotic pumps.

In film coatings, solid grades of polyethylene glycol can be used alone for the film-coating of tablets or can be useful as hydrophilic polishing materials.Polyethylene glycols are useful as plasticizers in

microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed into tablets.

Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets. The lubricant action is not as good as that of magnesium stearate and stickiness may develop if the material becomes too warm during compression. An antiadherent effect is also exerted, again subject to the avoidance of overheating.

Polyethylene glycols have been used in the preparation of urethane hydrogels, which are used as controlled-release agents. It has also been used in insulin-loaded microparticles for the oral delivery of insulin; it has been used in inhalation preparations to improve aerosolization; polyethylene glycol nanoparticles have been used to improve the oral bioavailability of cyclosporine; it has been used in self-assembled polymeric nanoparticles as a drug carrier; and copolymer networks of polyethylene glycol grafted with poly(methacrylic acid) have been used as bioadhesive controlled drug delivery formulations.

12. Regulatory status

Included in the FDA Inactive Ingredients Guide (dental preparations; IM and IV injections; ophthalmic preparations; oral capsules, solutions, syrups, and tablets; rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients

REVIEW OF LITERATURE

- **Robert G *et al*., (1990)** have patented fast dissolving dosage forms of Chlorpheniramine Maleate which disintegrate within ten seconds. Water soluble or water dispersible carrier materials were used in the group consisting essentially of mannitol in admixture with a natural gum, preferably acacia, guar gum, xanthan gum and tragacanth gum, pectin, algin, agar, carrageenan and gum Arabic. The mannitol constituted at least about 10 % by weight of the final dosing suspension and no more than about 15% by weight.

- **N Jaymin *et al.,* (1995)** have attempted to enhance the aqueous solubility and dissolution rate of Etoposide by solid state modifications using PEG of different molecular weights in various ratios. The co-precipitate of Etoposide with PEG 8000(1:10, PEG weight fraction of 0.91) increased its solubility 2 fold and dissolution rate 42 fold. The co-precipitate with PEGs (PEG 1500, PEG 3400 and PEG 6000) also increased Etoposide dissolution rate to great extent.

- **Franco *et al.,* (2001)** have studied dissolution properties and anticonvulsant activity of phenytoin-polyethylene glycol 6000 and polyvinylpyrollidone K-30 solid dispersions with different drug to carrier ratios were prepared by the solvent method. Among the various ratios, drug solubility and dissolution rate are improved by these formulations, particularly with SDPEG 1/20 and SDPVP 1/20 systems. Storage was found to influence the stability of the solid dispersions. . By maximal electroshock test, it was found that the intraperitoneal administration in mice of the SDPEG 1/20 and SDPVP 1/20 systems exhibited anticonvulsant activity similar to diphenylhydantoin sodium salt.

- **Shenoy *et al.*, (2003)** prepared and optimized fast dissolving tablets of Diclofenac sodium by direct compression method using superdisintegrants such as cross linked carboxymethylcellulose, sodium starch glycolate and cross linked povidone in different concentrations. Tablets containing cross linked carboxymethylcellulose showed better disintegrating character along with rapid release (90% drug release in 10 min).

- **Yamashita.k e*t al.*, (2003)** have established new preparation method for solid dispersion formulation of Tacrolimus using three different carriers like polyethylene glycol 6000 (PEG 6000), polyvinylpyrollidone (PVP) and hydroxypropylmethylcellulose (HPMC) were prepared by the conventional solvent method, in which Tacrolimus and the carrier was completely dissolved in the mixture of Dichloromethane and Ethanol. In new method solid dispersion of Tacrolimus was prepared without using dichloromethane as a solvent. The in vivo oral absorption study in dogs showed that bioavailability of Tacrolimus from SD with HPMC was remarkably improved compared with the crystalline powder. It was clarified that HPMC is the most appropriate carrier for SD of Tacrolimus. The physicochemical properties of SD with HPMC prepared by the new method were the same as those of SD prepared by the conventional solvent method. They concluded the pharmacokinetic parameters after oral administration in monkeys showed no significant difference (P >0.01) between solid dispersion s with HPMC prepared by the two methods.

- **Faham *et al.*, (2004)** have patented Orodispersible tablets containing Fexofenadine a synthetic antiallergic using mennitol as diluent(50 – 90 % w/w) and crospovidone as disintegrant(2-15 % w/w) and othe exipients like precipitated silica, sweetener and flavors.

- **Kashappa *et al.,* (2004)** have examined the enhancement of solubility of Valdecoxib using a series of hydrophilic carriers (mannitol,PEG 4000, PEG 6000, PEG 8000 and urea), surfactants (tween 20, tween 80 and sodium lauryl sulphate) and cosolvents (ethanol, methanol and glycol) at 37^0 c. The solubility of Valdecoxib could be enhanced significantly using PEG 4000 as a carrier, ethanol as cosolvent and SLS as a surfactant.

- **Patel DM *et al.,* (2004)** have demonstrated the use of factorial design in the formulation of Orodispersible tablets of Rofecoxib. Preliminary screening of three superdisintegrants namely sodium starch glycolate,crospovidone and croscarmellose sodium was carried out and crospovidone was found most effective giving lowest disintegration time and wetting time. The optimum concentration of crospovidone was found to be around 10 percent. Mannitol was incorporated as a diluent to improve palatability and to impart sweet taste as well as to keep the tablet weight. The percentage of crospovidone (X under one) and mannitol (X under two) were studied as independent variable. Wetting time and disintegration time were selected as independent variable(response y), based on multible linear regression analysis it was concluded that disintegration time and wetting time could be obtained when X1 is kept at high level and X2 is kept at low level.

- **Abdul RY *et al., (2005***) have patented instant dissolving tablet composition for Loratidine and Desloratidine. The invention was based on the choice of a novel disintegrant,PHARMABUST a proprietary formulation based on mannitol.instant dissolving tablets of loratidine and desloratidine was prepared by direct compression method.

- **Min-young heo *et al., (*2005)** have studied the effect of microemulsifying excipient in polyethylene glycol 6000 solid dispersion on enhanced dissolution and bioavailability of Ketaconazole. When the hydrophilic or lipophilic excipients were combined and incorporated into PEG based SDs a remarkable enhancement of the dissolution rate was observed. The PEG based SDs incorporating a self microemulsifying drug delivery system (SMEDDS) or (ME) were also useful at improving dissolution rate by forming a microemulsion or dispersible particles with the aqueous medium.

- **Patel M.M *et al.,(*2006)**, prepared solid dispersion of Valdecoxib with mannitol, polyethylene glycol 4000, and PVP K-12, were prepared with a view to increase its water solubility. Valdecoxib solid dispersion with PVP K-12 showed maximum drug release hence, the tablet formulation containing valdecoxib PVP K-12 solid dispersion, was prepared with a view to improve its water solubility.the drug release profile was studied in 0.1 N Hcl and the release profile was better than conventional marketed tablet.

- **Singh *et al.,* (2006)** have formulated and patented fast dissolving composition of various drugs with prolonged sweet taste. Preparation of non sugar sweetener in mucoadhesive form was prepared by using aspartame and mucoadhesive polymer such as PVM/MA copolymer,carbomer etc.This non sugar mucoadhesive sweetener was utilized to prepare fast dissolving tablets of Nimesulide,Ibuprofen,Cisapride and Cetrizine

- **Leonardi *et al*., (2007)** have studied dissolution properties of Prednisone by preparing SDs with PEG 6000 by solvent evaporation method. The SDs resulted in increased dissolution rate.

The improved dissolution rate was demonstrated by both X-ray diffraction and SEM, a decreased crystallinity of Prednisone. Tablets containing those SDs had dissolution profile that was better than those of CTs without PEG 6000.this indicated that PEG 6000 is a suitable excipient for the development of Prednisone fast release tablets.

- **Naveen *et al.,* (2007)** have studied enhancement of dissolution and mathematical modeling of drug release of a poorly water-soluble drug (Rofecoxib) using water-soluble carriers viz. polyethylene glycols (PEG 4000 and 6000), polyglycolized fatty acid ester (Gelucire 44/14), polyvinylpyrollidone K25 (PVP), poloxamers (Lutrol F127 and F68), polyols (mannitol, sorbitol), organic acid (citric acid) and hydrotropes. All the solid dispersions showed dissolution improvement vis-a`-vis pure drug to varying degrees, with citric acid, PVP and poloxamers as the most promising carriers. Solid-state characterization techniques revealed that distinct loss of drug crystallinity in the formulation, ostensibly accounting for enhancement in dissolution rate.

- **Swamy PV *et al.,* (2007)** have designed Orodispersible tablets of Meloxicam with a view to enhance pateient compliance. A combination of super disintegrant i.e, sodium starch glycolate-croscarmellose sodium or sodium starch glycolate-crospovidone were used along with directly compressible mannitol to enhance mouth feel. The formulation prepared by direct compression method using 2% w/w sodium starch glycolate and 1.5 % w/w croscarmellose sodium was found to be a better formulation ($t_{50\ \%}$ =22 min) based on in vitro release characteristics compared to conventional commercial tablet($t_{50\%}$ =68 min).

- **Sheetal *et al*., (2007)** developed a fast dissolving tablet of Oxcarbazepine containing Avicel PH 102 as adiluent and Ac-Di-sol as a superdisintegrant by wet granulation process. An effective,pleasant and stable formulation containing 12% Ac-Di-sol, 25% Avicel PH 102 and 8.5% starch as a binder was found to have a good hardness of 4-4.5 kg/cm^2 , disintegration time of 28±5 and drug release of not less than 90% within 30 min. the drug release was found to be comparable to the marketed dispersible tablet.

- **Madhuri *et al.,* (2008)** have prepared rapidly dissolving Ibuprofen SDs by low temperature melting method using PEG 6000. Characterized by SEM, DSC and FTIR. They were evaluated for solubility, in vitro release and oral bioavailability of Ibuprofen in rats. Quick release of Ibuprofen from SDs in rat intestine resulted in a significant increase in AUC and C_{max} and a significant decrease in T_{max} over pure Ibuprofen were noted.

- **Jigar *et al.*, (2008)** have prepared solid dispersions of Valdecoxib by melt granulation technique using PVP k 30 and PEG 4000 alone (1:1) and in combination (1:0.5:0.5).Phase solubility studies showed a linear increase in Valdecoxib solubility with increase in polymer concentration in both the cases. FTIR studies showed the stability of Valdecoxib and absence of well defined Valdecoxib-PVP k 30 – PEG 4000 interaction. Characterization by XRD and DSC indicated a complete transformation of drug from crystalline to amorphous form. In vitro dissolution studies in 0.1 N Hcl showed a significant enhance in the dissolution rate when PEG 4000 and PVP k 30 were used in combination.

- **Swamy PV *et al*., (2008),** attempted to prepare Orodispersible tablets of Carbamazepine with a view to enhance patient compliance by direct compression method using 3^2 full factorial design. Crospovidone (2-10% w/w) was used as superdisintegrant and microcrystallinecellulose (0-30% w/w) was used as diluent, along with directly compressible mannitol to enhance mouth feel. The tablets were evaluated for hardness, friability, thickness, drug content uniformity, *in vitro* dispersion time, wetting time and water absorption ratio. Based on *in vitro* dispersion time (approximately 10 s); the formulation containing 2% w/w crospovidone and 30%w/w microcrystalline cellulose was found to be promising and tested for in vitro drug release pattern (in pH 6.8 phosphate buffer), short-term stability (at 40º/75 % RH for 3 w) and drug-excipient interaction. This formulation showed four-fold faster drug release (t25%) compared to the conventional commercial tablet formulation. Short-term stability studies on the formulation indicated that there are no significant changes in drug content and in vitro dispersion time ($p < 0.05$).

- **Venkatesh DP *et al.,* (2008)** have attempted to mask the taste of Ambroxol hydrochloride a bitter drug and to formulate into a Orodispersible tablet by complexation with ion exchange resins, which also acts as super disintegrating agents. Cation exchange resins like Indion-204 and Indion-234 were utilized for the sorption of drug. Drug-resinates was prepared in drug to resin ratio of 1:5 and 1:6. Tablets with both the resins have shown quick disintegrating features, i.e., within 20 s, which is very characteristic of Orodispersible tablets. Also, the dispersion not showing any bitter taste, indicate the capability of ion exchange resins used, both as taste masking and super disintegrating agents. Almost more than 90 percent of drug was released from both the formulations within 1 hour.

- **Mallikarjuna C *et al.,* (2008)** developed fast dispersible Aceclofenac tablets and studied the functionality of superdisintegrants such as croscarmellose sodium, sodium starch glycolate and crospovidone. on wetting time, disintegration and *in vitro* dissolution profile. Disintegration time and dissolution parameters($t_{50\%}$ and $t_{90\%}$) decreased with increase in the level of croscarmellose sodium.

- **Patel DM *et al.,* (2008)** attempted to optimize the fast dissolving Etoricoxib tablets prepared by sublimation technique. Granules containing Etoricoxib, menthol, crospovidone, aspartame and mannitol were prepared by wet granulation. Menthol was sublimed from the granules by exposing the granules to vaccum. The porous granules were then compressed in to tablets. Alternatively, tablets were prepared first and later exposed to vacuum. A 3^2 full factorial design was applied to investigate the combined effect of 2 formulation variables: amount of menthol and crospovidone.

MATERIALS AND EQUIPMENTS

Table 3: Materials used

Name of the materials	Name of company
Domperidone	Carewell pharma, Chennai
PEG 4000	Sisco research lab pvt ltd
PEG 6000	Himedia lab pvt ltd
PEG 8000	Himedia lab pvt ltd
Dimetthylformamide	Qualigens fine chemicals
Methanol	SD fine chem. Ltd
Ammonium acetate	SD fine chem. Ltd
Dioxane	SD fine chem. Ltd
Glacial acetic acid	Qualigens fine chemicals
Hydrochloric acid	SD fine chem. Ltd

Table 4: Equipments used

Name of equipment	Name of company
Vacuum pump	Gelman sciences
Dissolution apparatus	Labindia Disso 2000
UV spectrometer	Jasco V 530
Alphadigidoc TM	Alpha Innotech corporation
FT IR spectrometer	(Jasco-FT-IR 8201 PC)
pH tester 1 (water proof)	Oakton instruments.

ANALYTICAL METHOD

Domperidone a prokinetic drug used in the treatment of nausea and vomiting chemically known as 6-chloro-3-[1-[3-(2-oxo-3H-benzimidazol-1-yl) propyl] piperidin-4-yl] -1H-benzimidazol-2-one.The estimation of Domperidone in the formulations can be done by various HPLC,HPTLC and spectrophotometric methods.

Methods for the estimation of Domperidone in tablet formulation

- HPLC method

This method allows the determination of 100- 500 ng/spot of Domperidone using mobile phase composition as n-butanol: glacial acetic acid: water (9.3: 0.25: 0.5, v/v/v). When densitometric analysis carried out in the absorbance mode at 288 nm, the Rf value will be 0.21, limit of detection 30 ng/spot and limit of quantification 65 ng/spot[Susheel.J.V,et al., 2007].

- HPTLC method

This method allows determining Domperidone on aluminium sheets of silica gel 60 F_{254} using ethyl acetate: methanol: benzene (40:20:40 v/v) as mobile phase at a linear concentration range of 120-360 ng/spot. The limit of detection 40.53 ng/spot. Mean analytical recovery in Domperidone capsules 99.48± 1.15 [Bhavesh P.,et al,2007].

- UV spectrophotometric method

Domperidone can be estimated from solid dosage forms by UV spectrophometric method at λ_{max} 284 nm. Beer's law linearity range is 8 -30 mcg/ml [Prabu SL.,et al, 2008].

ANALYTICAL METHODOLOGY USED IN THE PRESENT STUDY

Procedure for standard graph preparation of Domperidone BP 1996

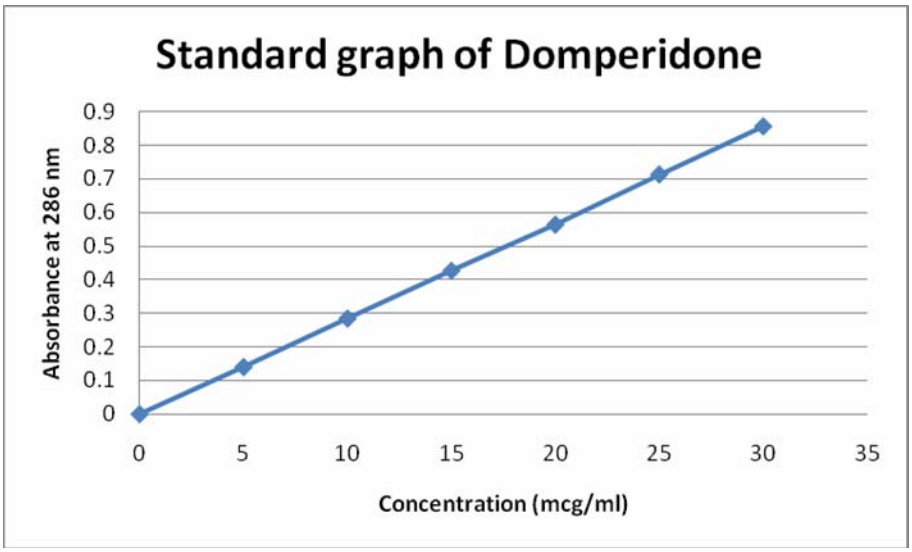
Accurately weighed 100 mg of Domperidone was dissolved in 100 ml of methanol taken in a properly cleaned and dried volumetric flask. From this solution 10 ml is made up to 100 ml with methanol which will give the stock solution 100 mcg/ml.

From this solution pipette out 0.5,1.0,1.5,2.0,2.5 and 3.0 ml, which were transferred into a series of 10 ml volumetric flasks and the final volume was brought up to 10 ml with 0.1 M HCl to get a concentration of 5-30 mcg/ml. A blank was also prepared. The absorbance was measured at 286 nm and the standard graph was plotted against concentration (mcg/ml) Vs absorbance. The results were given in Table 5 and Figure 2.

Table 5 : Standard graph of Domperidone

Concentration (mcg/ml)	Absorbance at 286 nm
0	0.000
5	0.140
10	0.284
15	0.426
20	0.563
25	0.712
30	0.855

Figure 2: Standard graph of Domperidone at 0.1 M HCl



EXPERIMENTAL METHODOLOGY

Domperidone a prokinetic dopamine receptor antagonist indicated for the treatment of nausea and vomiting. As Domperidone is practically in soluble in water the absorption is dissolution rate limited. Solid dispersion technology can be used to improve the *in vitro* and *in vivo* dissolution properties of poorly soluble drugs.PEG 4000,PEG 6000 and PEG 8000 were used as carriers in the preparation of Domperidone solid dispersion in the ratios of 1:1, 1:3 and 1:9 by solvent evaporation method using Dimethylformamide (DMF) as solvent.

Procedure for preparation of Domperidone solid dispersion by Solvent evaporation method

Respective amount of carrier was dissolved in required amount of DMF taken in a conical flask to get a clear completely soluble polymer DMF solution, magnetic stirrer was used for this purpose. The weighed amount of Domperidone was added to this solution carefully with constant stirring. Stirring was continued until the drug was completely incorporated in solvent. Then the solvent was removed by evaporation at 40° C under vacuum. The mass obtained was dried, crushed, pulverized and sifted through mesh no. 80.The details were given in Table 6.

Physical mixture (PM)

Drug: Carrier ratio of 1:1 was used to prepare physical mixture (1000 mg of drug and 1000 mg of carrier). The drug and carrier were mixed thoroughly in a mortar. This was done by geometric dilution technique to ensure homogenous distribution.

Table 6: Drug carrier ratio and respective amount taken

Solid dispersion	Drug carrier ratio	Drug (mg)	Carrier (mg)
Domperidone-PEG 4000	1:1	1000	1000
	1:3	500	1500
	1:9	200	1800
Domperidone-PEG 6000	1:1	1000	100
	1:3	500	1500
	1:9	200	1800
Domperidone-PEG 8000	1:1	1000	100
	1:3	500	1500
	1:9	200	1800

CHARACTERIZATION AND EVALUATION OF DOMPERIDONE SOLID DISPERSION

a. Thin layer Chromatography
b. IR spectral Analysis
c. Powdered X-ray Diffraction studies
d. Differential Scanning Calorimetry
e. Scanning electron microscopy
f. Drug content uniformity
g. *In vitro* dissolution studies

Thin layer chromatography (TLC)

A thin layer chromatographic method was also carried to study the interaction between the drug and carriers and also to confirm the chemical satiability of the solid dispersions prepared. For this, the pure drug and the solid dispersions prepared with various carriers by solvent evaporation method were subjected to chromatographic studies **British Pharmacopoeia 1996**.

The TLC system used for this study is given below.

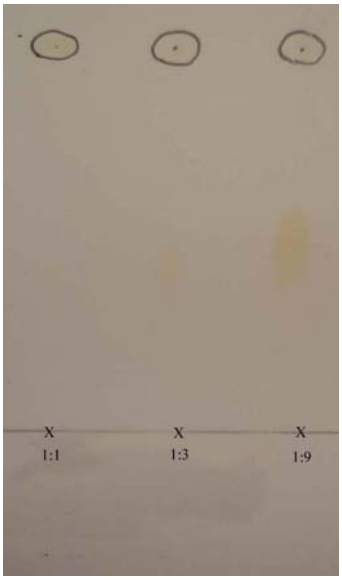
Precoated TLC Plates Ltd, Mumbai	:	Manufactured by SD Fine chemicals
Adsorbent Layer	:	Silica gel GF 254.
Layer Thickness	:	250 &μm.
Separation technique	:	Ascending
Chamber Saturation	:	The chamber was lined on three sides with filter paper and saturated for 30 minutes.
Mobile phase	:	Methanol: Dioxan: Ammonium acetate solution [40:40:20 % v/v][90].
Preparation of sample	:	A suitable amount of pure drug or equivalent solid dispersion dissolved in Methanol and used for spotting.
Amount applied	:	5 μl.
Detection	:	Dry the plate in a current of warm air for 15 min and expose it to iodine vapor until the spot appear. Examine in day light.

The Rf values obtained were given in the Table 7 and thin layer chromatograms of various solid dispersions were shown in Figure 3.

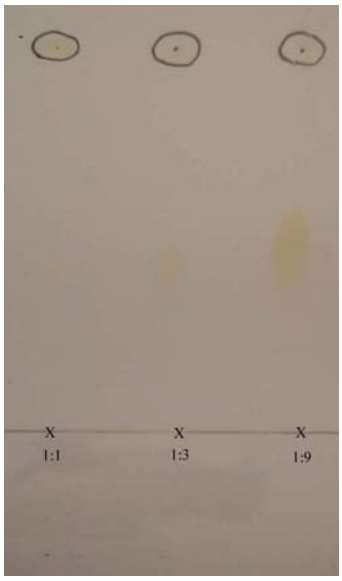
Table 7: TLC data for various solid dispersions systems

Solid dispersion	Drug carrier ratio	Rf value	No of spots
Pure Domperidone	---	0.70	single
Domperidone-PEG 4000	1:1	0.71	single
	1:3	0.71	single
	1:9	0.71	single
Domperidone-PEG 6000	1:1	0.70	single
	1:3	0.70	single
	1:9	0.71	single
Domperidone-PEG 6000	1:1	0.70	single
	1:3	0.71	single
	1:9	0.71	single

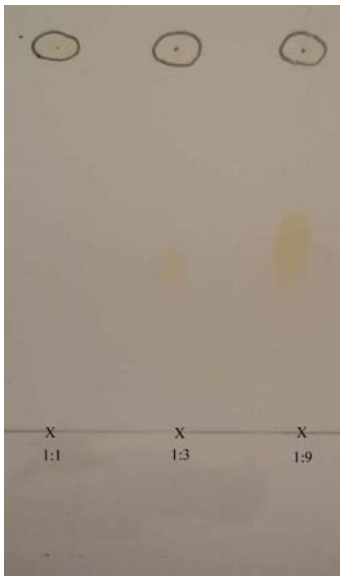
Pure Domperidone



DOM- PEG 4000 SD



DOM- PEG 6000 SD



DOM- PEG 8000 SD

Figure 3: Thin layer chromatogram of various solid dispersions

IR SPECTRAL ANALYSIS

Fourier Transform (FTIR) spectra of the samples were obtained in the range of 400-4000 cm^{-1} using a Jasco-FT-IR 8201 PC Spectrophotometer (Jasco.Essex) by the KBr disc method. The IR Spectra obtained are given in Figure 4 - 8.

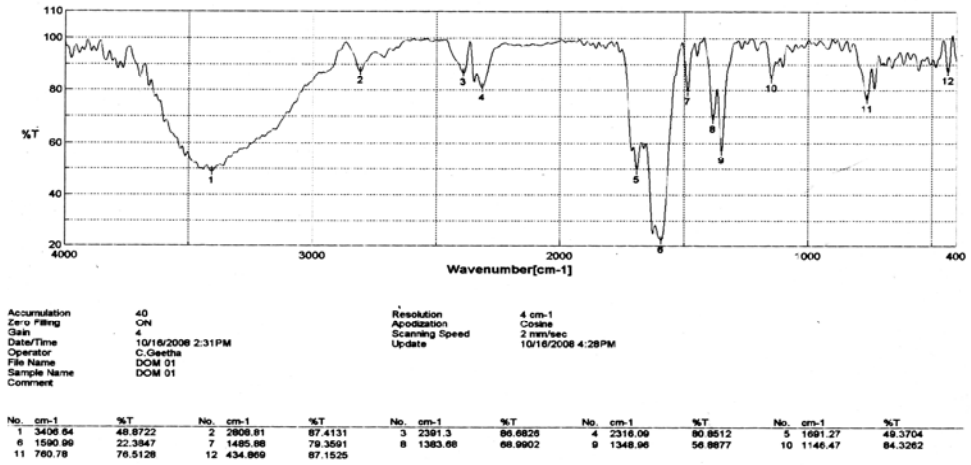


Figure 4: IR spectrum of pure Domperidone

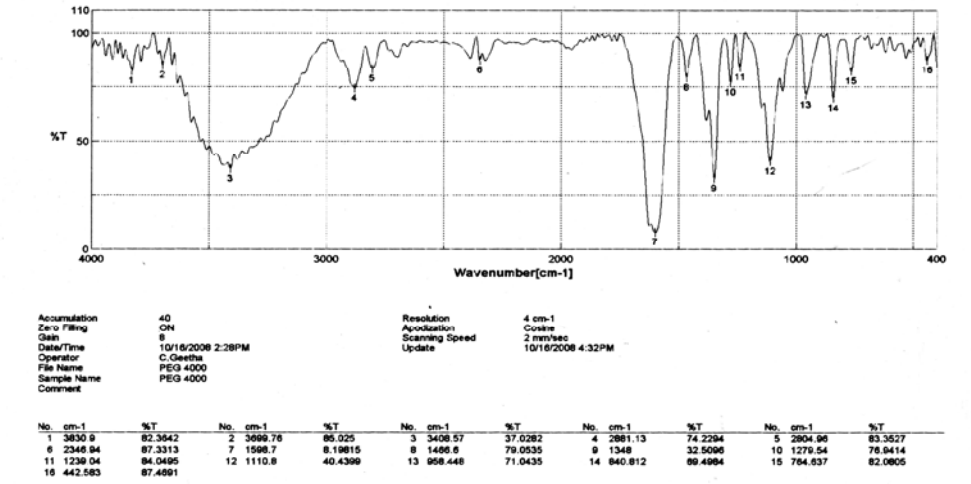
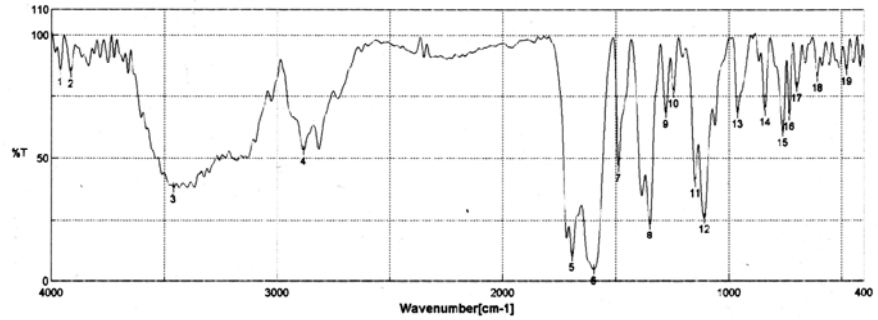


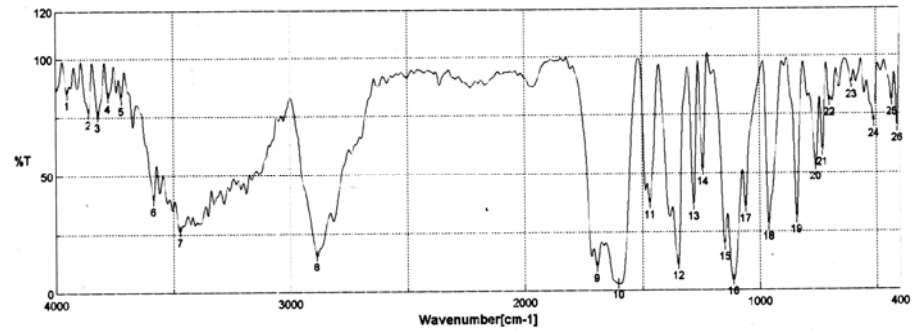
Figure 5: IR spectrum of pure PEG 4000



Accumulation	40
Zero Filling	ON
Gain	8
Date/Time	10/16/2008 0:45PM
Operator	C.Geetha
File Name	PEG 4000 (1,1)
Sample Name	PEG 4000 (1,1)
Comment	
Resolution	4 cm-1
Apodization	Cosine
Scanning Speed	2 mm/sec
Update	10/16/2008 4:34PM

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3951.07	84.9937	2	3914.79	84.4077	3	3459.67	38.0386	4	2883.06	53.3268	5	1693.19	9.94965
6	1596.77	4.76717	7	1487.81	46.2846	8	1348.96	23.2005	9	1278.57	68.4966	10	1243.86	76.4704
11	1148.4	40.1763	12	1107.9	25.879	13	961.341	68.4586	14	838.883	89.3251	15	759.816	60.963
16	730.889	67.4586	17	698.105	78.6004	18	608.431	82.6686	19	478.26	85.3768			

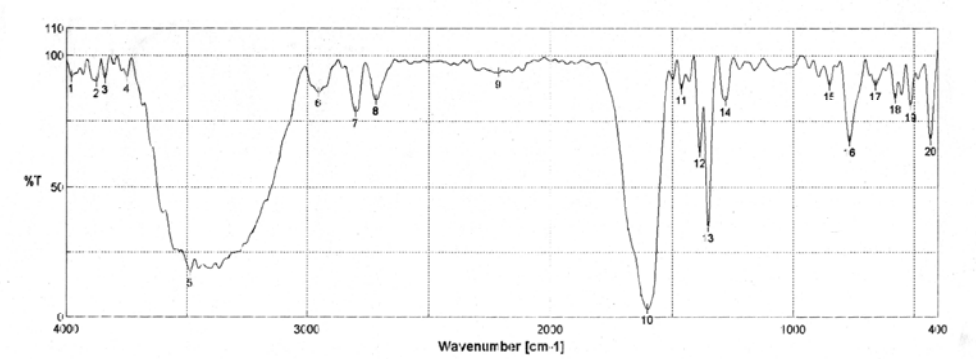
Figure 6: IR spectrum of solid dispersions of Domperidone with PEG 4000 (1:1)



Accumulation	40
Zero Filling	ON
Gain	16
Date/Time	10/16/2008 0:29PM
Operator	C.Geetha
File Name	PEG 4000 (1,3)
Sample Name	PEG 4000 (1,3)
Comment	
Resolution	4 cm-1
Apodization	Cosine
Scanning Speed	2 mm/sec
Update	10/16/2008 4:37PM

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3952.39	84.7162	2	3856.83	76.5224	3	3820.29	75.3118	4	3775.94	83.441	5	3720.01	82.3338
6	3584.06	39.3943	7	3472.2	26.3115	8	2886.91	15.6588	9	1693.19	10.26	10	1603.52	3.12825
11	1468.53	37.0489	12	1347.03	10.982	13	1280.5	36.4415	14	1240.97	50.9138	15	1148.4	19.3344
16	1111.76	4.3283	17	1059.69	35.2273	18	961.341	27.7227	19	841.776	30.568	20	759.816	52.9516
21	730.889	59.3317	22	700.998	80.384	23	606.503	87.7947	24	511.044	71.2066	25	433.905	80.4047
26	410.763	69.2053												

Figure 7: IR spectrum of solid dispersions of Domperidone with PEG 4000 (1:3)



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	10/12/2007 4:18PM	Update	11/16/2007 10:33AM
Operator	C.Geetha		
File Name	SE pvp40(1:9)		
Sample Name	SE pvp40(1:9)		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3679.39	91.9821	2	3877.18	90.145	3	3841.51	91.459	4	3752.3	91.9512	5	3486.67	17.6125
6	2956.34	89.238	7	2864.96	78.4921	8	2719.14	83.0874	9	2210.32	93.5778	10	1599.68	3.44663
11	1461.78	87.5309	12	1383.98	53.3417	13	1348	34.6687	14	1276.35	82.7189	15	848.525	68.8868
16	767.53	67.4121	17	661.464	88.7551	18	579.504	83.7726	19	514.901	80.6596	20	431.977	67.8784

Figure 8: IR spectrum of solid dispersions of Domperidone with PEG 4000 (1:9)

Powder X-ray diffractometry

X-Ray Powder Diffractometry is one of the most powerful and established technique for material structural analysis, capable of providing information about the structure of a material at the atomic level. Low and High temperature measurement facilities are available **Chidavaenzi O.C and Buckton G,2001**.

The Temperature attachment enables analysis from -170^{o}C to +450^{o}C under vacuum. Change in unit cell dimensions, structural changes at phase transitions etc, as a function of temperature can be determined. The Powder X-ray Diffraction Patterns were recorded using Bruker AXS D8 advance instrument for pure Domperidone, and solid dispersions of DOM-PEG 4000 (1:1,1:3 and 1:9) were carried out and the results were given in Figure 9 - 12 .

The specifications of the instrument were given below

Make/Model	:	Bruker AXS D8 Advance
Configuration	:	Vertical, Theta/2 Theta geometry
Measuring circle diameter	:	435, 500, and 600 mm predefined
Angle range	:	360°
Max. Usable angular range:	:	3° to 135°
Smallest addressable increment	:	0.001°
Max. angular speed	:	30°/s
X-ray source	:	Cu, Wavelength 1.5406 A°
Detector	:	Si(Li) PSD
Temperature attachment Make /Model	:	Anton Paar, TTK 450
Temperature Range	:	-170 °C to +450 °C

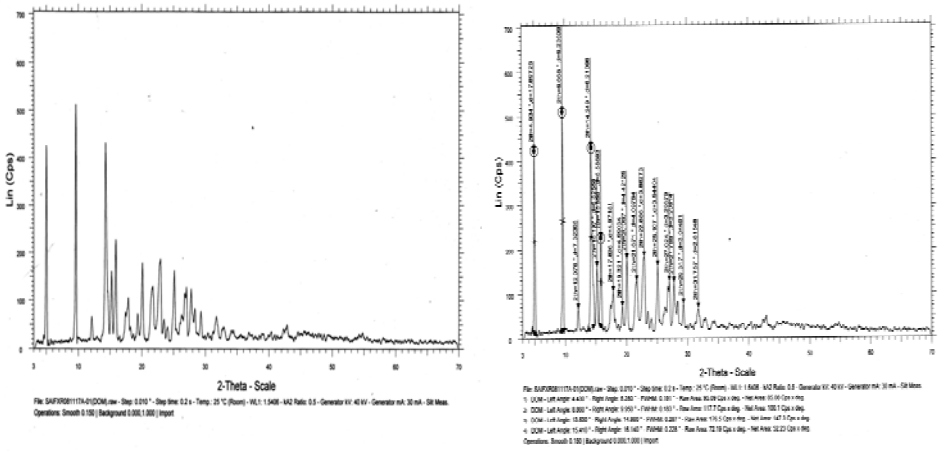


Figure 9: X- ray diffraction studies of pure Domperidone

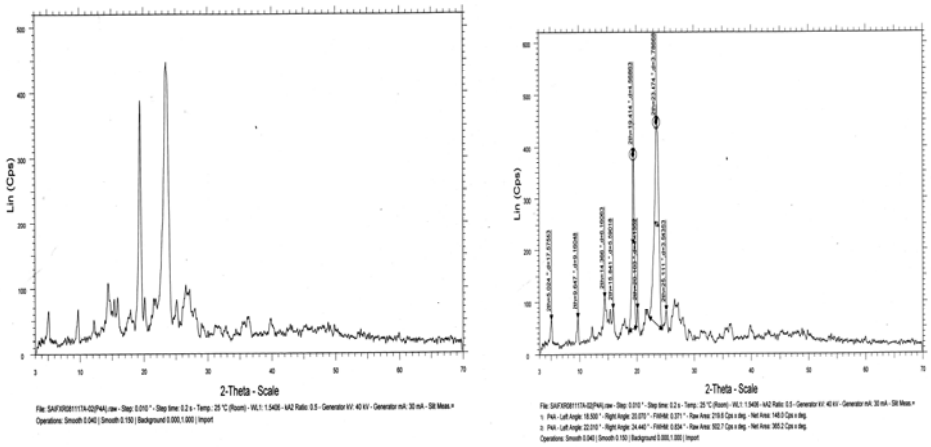


Figure 10: X- ray diffraction studies of solid dispersions of Domperidone with PEG 4000(1:1)

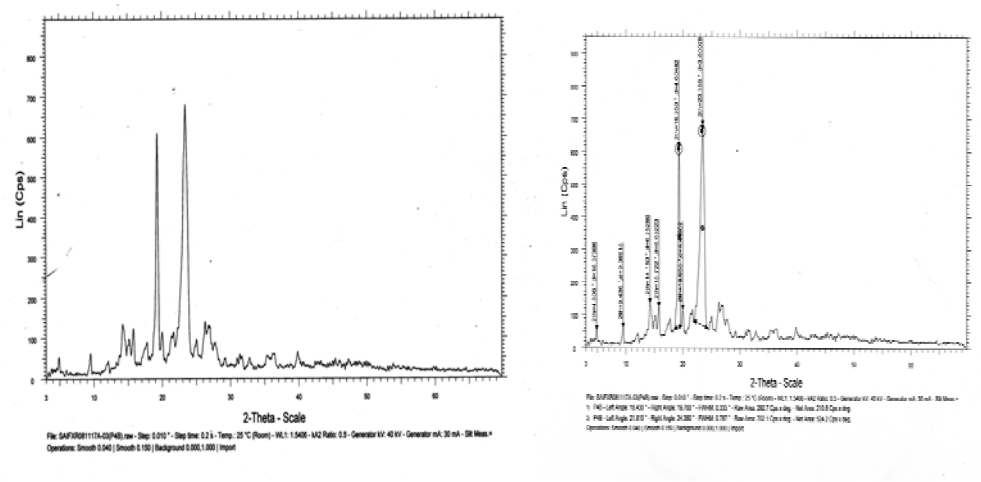


Figure 11: X- ray diffraction studies of solid dispersions of Domperidone with PEG 4000 (1:3)

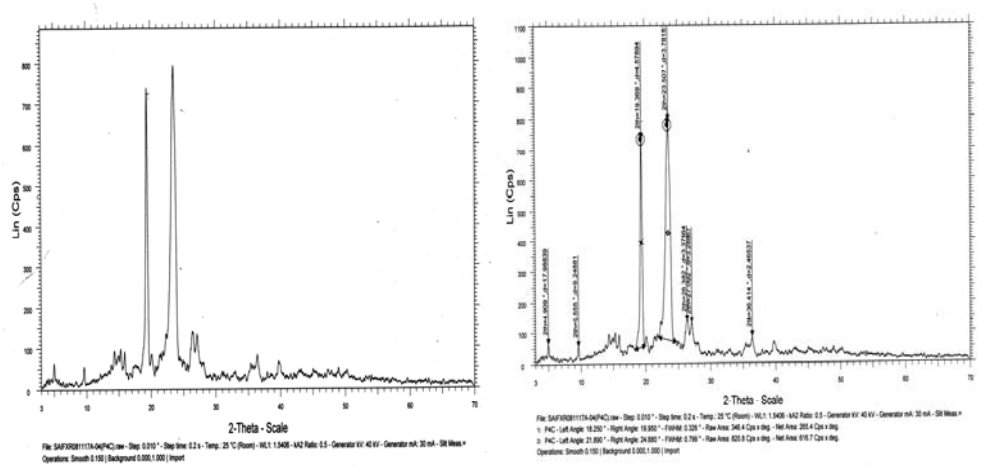


Figure 12: X- ray diffraction studies of solid dispersions of Domperidone with PEG 4000(1:9)

Differential Scanning Calorimetry

DSC (Differential Scanning Calorimetry) measures the amount of heat energy absorbed or released by a sample, as it is heated, cooled or held at a constant temperature. The DSC thermograms were taken for pure Domperidone and solid dispersions of DOM-PEG 4000(1:1, 1:3 and 1:9) and were given in Figure 13 – 17.The specifications of the instrument were given below

Make/Model	:	Mettler Toledo DSC 822e
Temperature Range	:	-150 °C to max. 700°C
Measurement range	:	± 350 mW at RT
Measurement resolution	:	0.04 mW at RT
Temperature Accuracy	:	± 0.2°C
Temperature reproducibility	:	± 0.1°C
Heating rate	:	RT to 700°C in 7 min
Cooling rate	:	+ 100°C to – 100°C in 15 min
Sampling rate	:	Max 10 values / sec

The applications of DSC are numerous, either for routine quality control measurements or in research, where high sensitivity and flexibility are important aspects.Applications include study of melting behavior, glass transition, specific heat anomaly, oxidation stability, chemical kinetics etc **Corrigan.D.O, Healy.A.M,2002**.

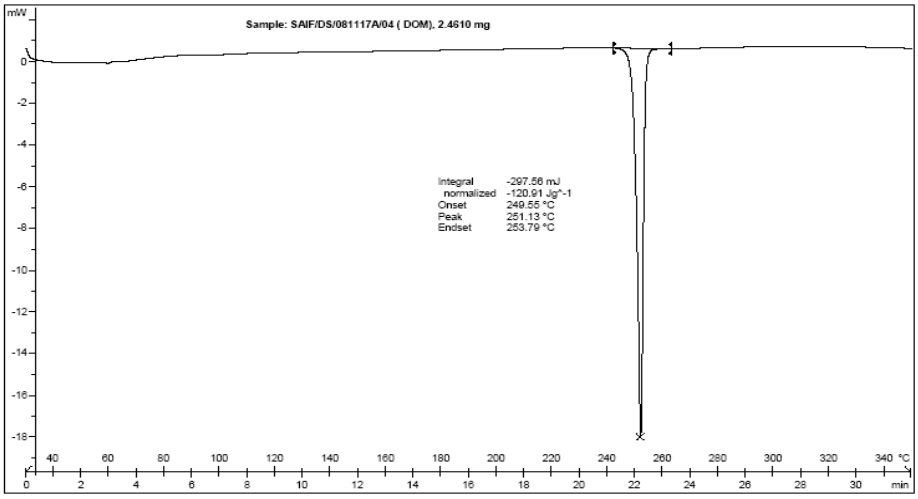


Figure 13: DSC Thermogram of pure Domperidone

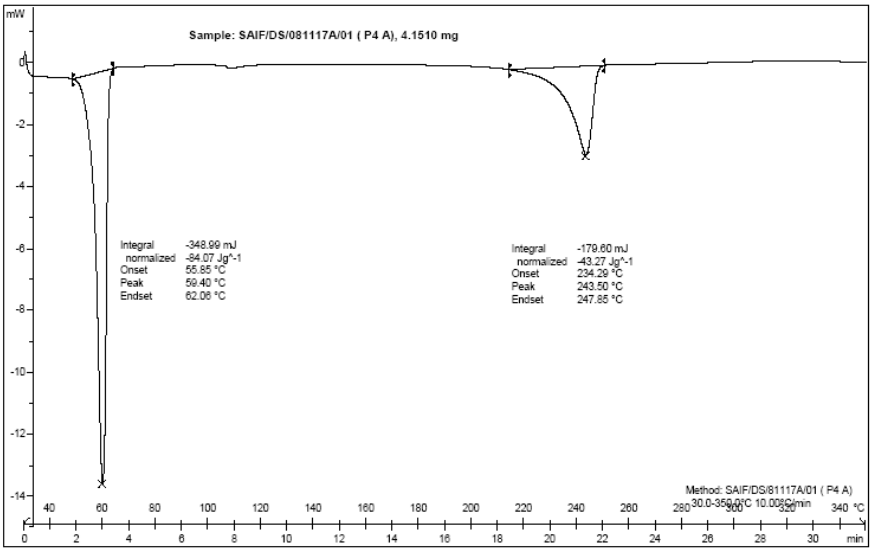


Figure 14: DSC Thermogram of solid dispersion of Domperidone with PEG 4000 (1:1)

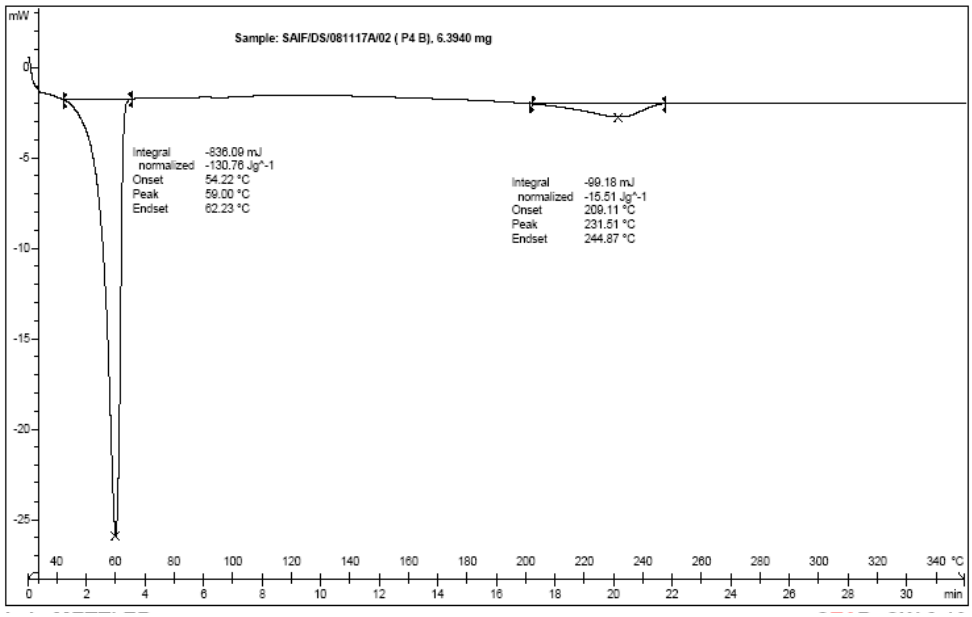


Figure 15: DSC Thermogram of solid dispersion of Domperidone with PEG 4000 (1:3)

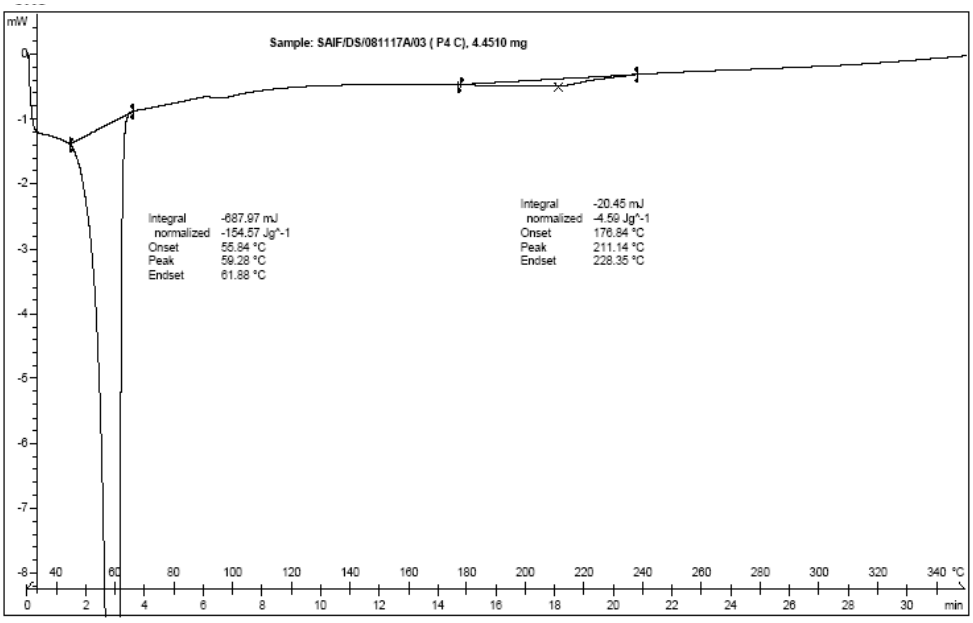


Figure 16: DSC Thermogram of solid dispersion of Domperidone with PEG 4000 (1:9)

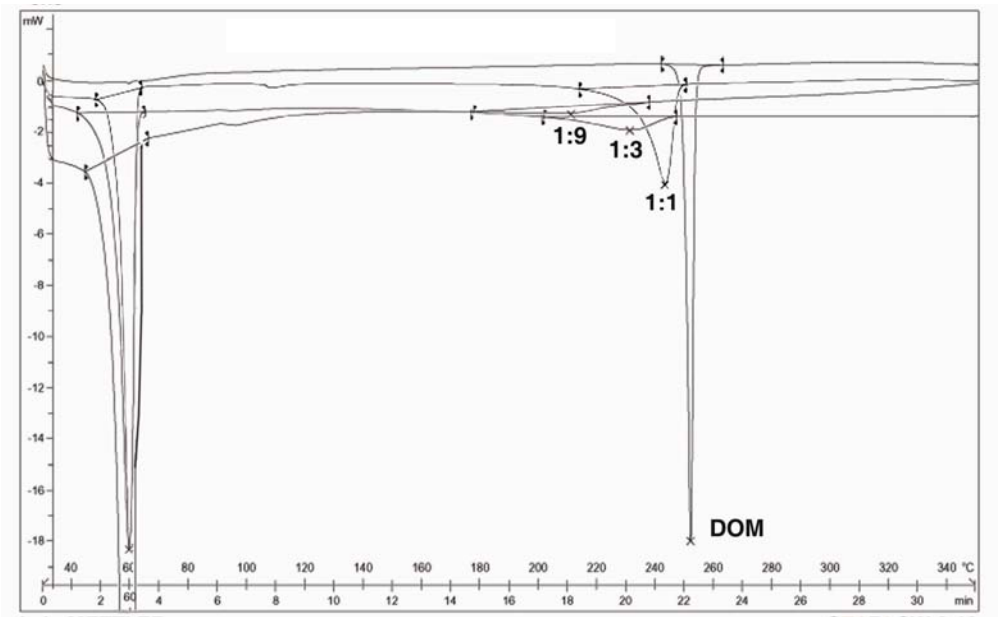


Figure 17: DSC Thermograms of pure drug and solid dispersions

Scanning Electron Microscopy

Scanning electron microscopy (SEM) is a method for high resolution surface imaging. The SEM uses an electron beam for surface imaging. The advantages of SEM over light microscopy are greater magnification and much larger depth of field. The morphological characteristics of pure Domperidone and solid dispersion DOM-PEG 4000(1:1) were studied using the SEM[Foster.T.P and Leatherman.M.W,1995]. The SEM results were shown in Figure 18 and 19.

Specifications of SEM-EDS used for the analysis follows.

SEM Make : JEOL Model JSM – 6390LV

EDS Make : JEOL Model JED – 2300

Resolution	:	3 nm (Acc V 30 KV, WD 8 mm, SEI)
	:	8 nm(Acc V 3.0 KV, WD 6 mm, SEI)
	:	15 nm(Acc V 1.0 KV, WD 6 mm, SEI)
Magnification	:	5 × to 300, 000 × (Both in High and Low Vacuum Modes)
Image Modes		SEI, BEI
Probe Current	:	1 pA to 1mA
High vacuum resolution		3 nm
Low vacuum resolution		4 nm
Specimen Stage		
Type		Eucentric
Manual type		5 Axes (X, Y, Z, R, T), Manual Control
Tilt		+90º
Specimen holder		10 mm diameter.
Maximum loadable specimen size	:	1

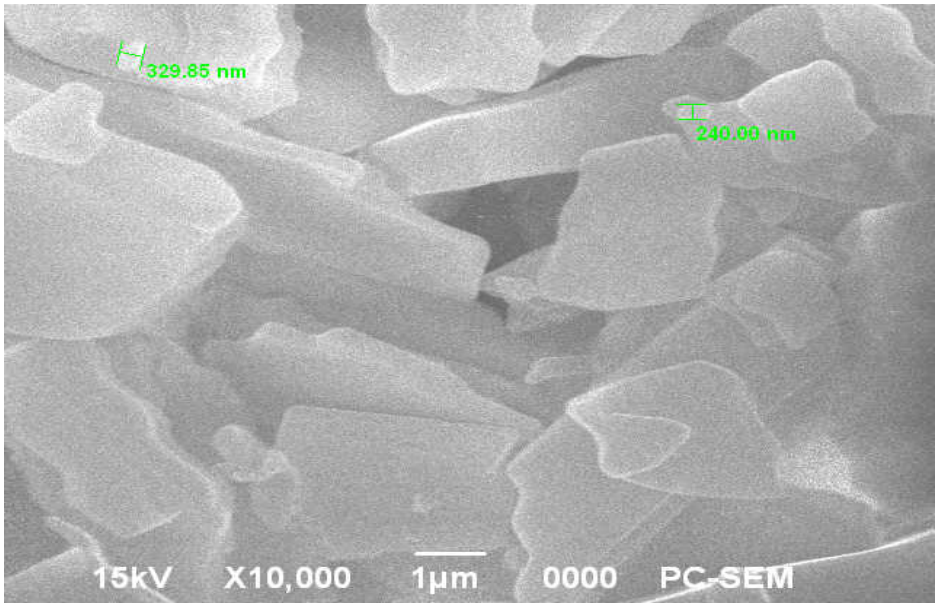


Figure 18: SEM of pure Domperidone (10000 X)

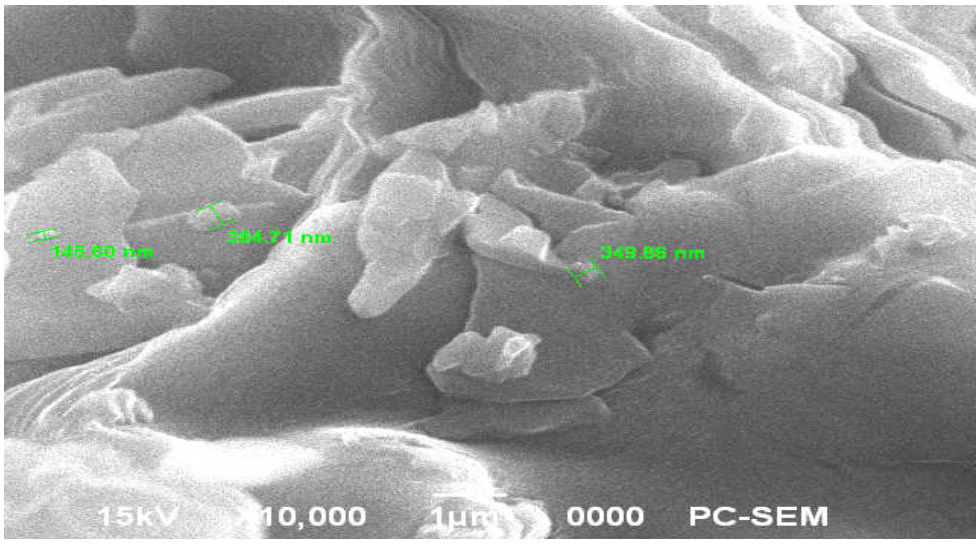


Figure 19: SEM of Domperidone PEG 4000 SD (1:1) (10000 X)

DRUG CONTENT UNIFORMITY

The prepared Domperidone solid dispersion was tested for drug content uniformity. From each batch of solid dispersion prepared in different ratios, solid dispersion equivalent to 10mg of Domperidone were taken and analyzed for drug content uniformity.

Estimation of Domperidone in solid dispersion by UV Spectroscopy

Accurately weighed amount of Domperidone solid dispersion was dissolved in 100 ml of 0.1M HCl in 100ml volumetric flask which was previously clean and dry. This solution after suitable dilution was measured for absorbance at 286 nm in a Jasco V530 UV visible spectrophotometer. The results were shown in Table 8.

Table 8: Drug content uniformity in Domperidone SDs

Solid dispersion	Drug : carrier	Amount of SD taken(mg)	Expected amount of Domperidone in SD (mg)	Domperidone estimated by spectrophotometer (%)
Domperidone PEG 4000	1:1	20	10	98.57±1.45
	1:3	40	10	100.19±0.76
	1:9	100	10	101.84±0.48
Domperidone PEG 6000	1:1	20	10	99.48±0.93
	1:3	40	10	101.96±0.82
	1:9	100	10	99.78±0.59
Domperidone PEG 8000	1:1	20	10	102.67±0.71
	1:3	40	10	102.53±0.44
	1:9	100	10	101.6±0.35

n = 3 ±, Sd

***In vitro* dissolution studies**

The dissolution studies are the most important part of the evaluation of solid dispersion, where the dissolution of pure drug and solid dispersion is carried out. Dissolution rate studies of various solid dispersions were carried out in 0.1 M HCl using USP XXII dissolution apparatus (labIndia Disso 2000).

Dissolution method

900 ml of 0.1 M HCl was used as dissolution medium. SDs equivalent to 10 mg of Domperidone was taken in a hard gelatin capsule; a stainless steel wire was wound around the capsule to sink. The paddle type stirrer was adjusted to 50 rpm. The temperature was maintained at 37°±2°c. 5 ml aliquot dissolution media was withdrawn at different time intervals and volume withdrawn was replaced with fresh quantity of dissolution medium. The samples were analyzed for Domperidone after suitable dilution by measuring the absorption values at 286 nm using Jasco V 530 UV visible spectrophotometer, 0.1 M HCl was used as a blank. The percentage of Domperidone dissolved at various time intervals was calculated and plotted against time. T_{50}, T_{90} values were calculated from these dissolution curves. The results are shown in Table 9-12 and Figure 21-24.

Figure 20: Dissolution apparatus (Labindia Disso 2008)

Table 9: Dissolution profile of Domperidone from PEG 4000 solid dispersion at different drug carrier ratios

Time in minutes	Percentage release of Domperidone from different drug carrier ratios				
	Pure drug 10 mg	Physical mixture	1:1	1:3	1:9
0	0	0	0	0	0
5	2.78±0.39	16.33±1.40	27.00±0.52	21.83±1.42	23.85±0.76
15	8.41±0.74	49.08±0.86	81.05±0.66	65.56±0.90	74.64±0.12
30	15.10±0.46	73.80±0.91	88.62±0.14	89.04±0.39	97.39±0.09
45	24.96±0.62	74.33±1.34	89.29±0.63	90.37±0.56	98.76±0.86
60	31.09±1.2	78.37±1.21	95.77±0.72	92.15±0.78	99.12±1.56

n = 3,± Sd

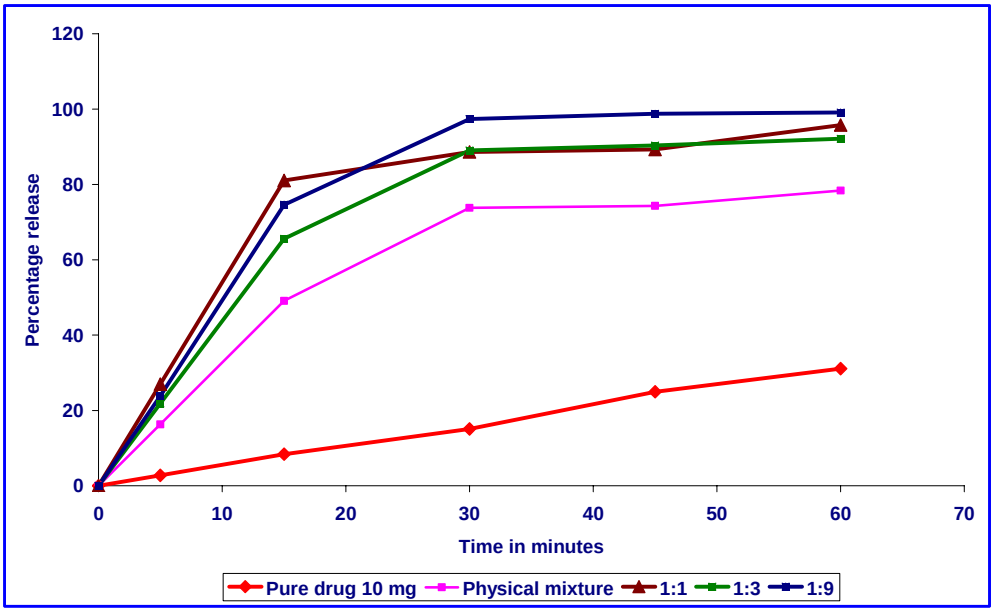


Figure 21: Dissolution profile of Domperidone from PGE 4000 solid dispersion at different drug carrier ratios

Table 10: Dissolution profile of Domperidone from PGE 6000 solid dispersion at different drug carrier ratios

Time in minutes	Percentage release of Domperidone from different drug carrier ratios				
	Pure drug 10 mg	Physical mixture	1:1	1:3	1:9
0	0	0	0	0	0
5	2.78±0.39	15.42±1.20	18.87±1.56	16.68±0,91	25.73±0.14
15	8.41±0.74	48.51±0.52	44.28±0.39	50.13±1.34	77.28±0.63
30	15.10±0.46	50.87±0.63	56.44±0.74	90.38±1.21	97.79±0.72
45	24.96±0.62	53.02±0.86	62.49±0.46	97.28±0.52	98.58±0.12
60	31.09±1.2	55.87±0.12	72.09±0.72	98.13±0.66	99.31±0.76

n = 3,± Sd

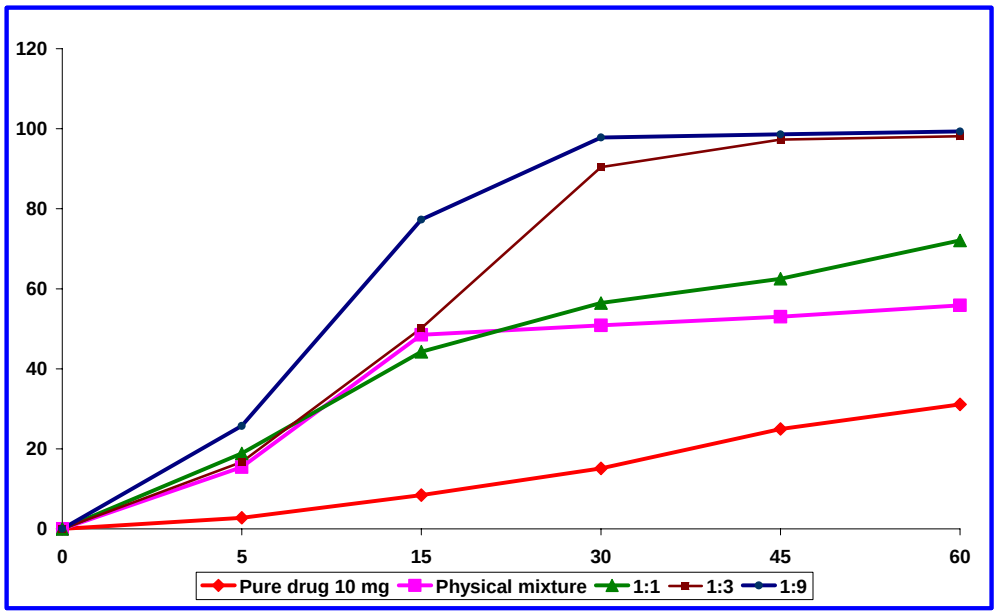


Figure 22: Dissolution profile of Domperidone from PEG 6000 solid dispersion at different drug carrier ratios

Table 11: Dissolution profile of Domperidone from PEG 8000 solid dispersion at different drug carrier ratios

Time in minutes	Percentage release of Domperidone from different drug carrier ratios				
	Pure drug 10 mg	Physical mixture	1:1	1:3	1:9
0	0	0	0	0	0
5	2.78±0.39	13.68±1.56	16.82±0.98	18.27±0.68	28.48±1.60
15	8.41±0.74	47.67±1.33	51.29±0.65	54.82±1.56	85.48±1.72
30	15.10±0.46	52.95±2.10	59.87±0.83	76.68±0.73	96.36±0.56
45	24.96±0.62	58.83±1.12	64.38±1.20	78.48±0.82	97.74±0.62
60	31.09±1.2	62.49±1.84	74.56±0.95	80.06±1.34	99.36±1.50

n = 3,± Sd

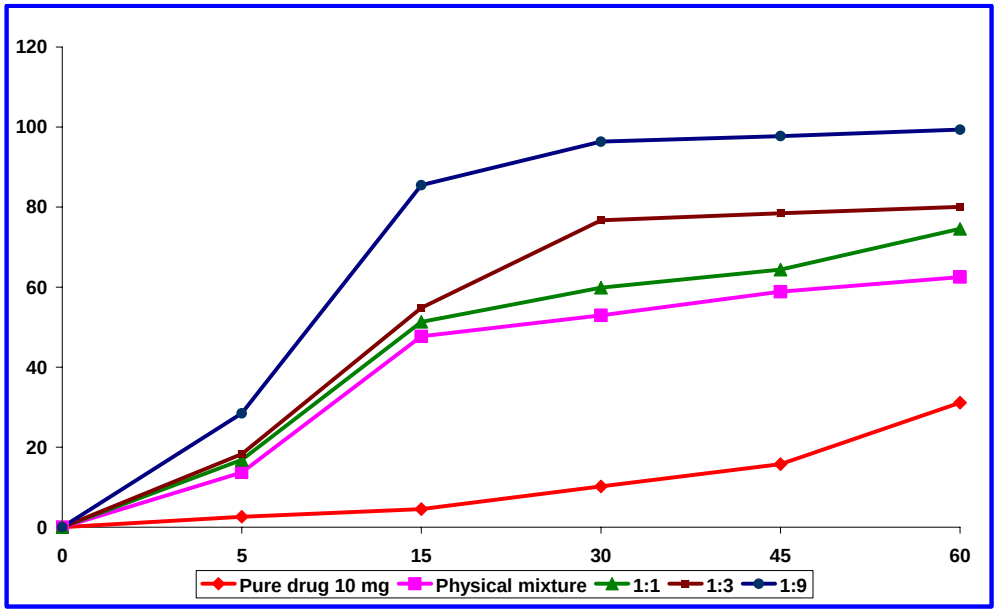


Figure 23: Dissolution profile of Domperidone from PEG 8000 solid dispersion at different drug carrier ratios

Table 12: Percentage release of Domperidone from various solid dispersions

Time in minutes	Percentage release of Domperidone from									
	Pure drug	DOM: PEG 4000			DOM: PEG 6000			DOM: PEG 8000		
		1:1	1:3	1:9	1:1	1:3	1:9	1:1	1:3	1:9
0	0	0	0	0	0	0	0	0	0	0
5	2.6	27.00	21.83	23.85	18.87	16.68	25.73	16.82	18.27	28.48
15	4.5	81.05	65.56	74.64	44.28	50.13	77.28	51.29	54.82	85.48
30	10.2	88.62	89.04	97.39	56.44	90.38	97.79	59.87	76.68	96.36
45	15.75	89.29	90.37	98.76	62.49	97.28	98.58	64.38	78.48	97.74
60	31.09	95.77	92.15	99.12	72.09	98.13	99.31	74.56	80.06	99.36

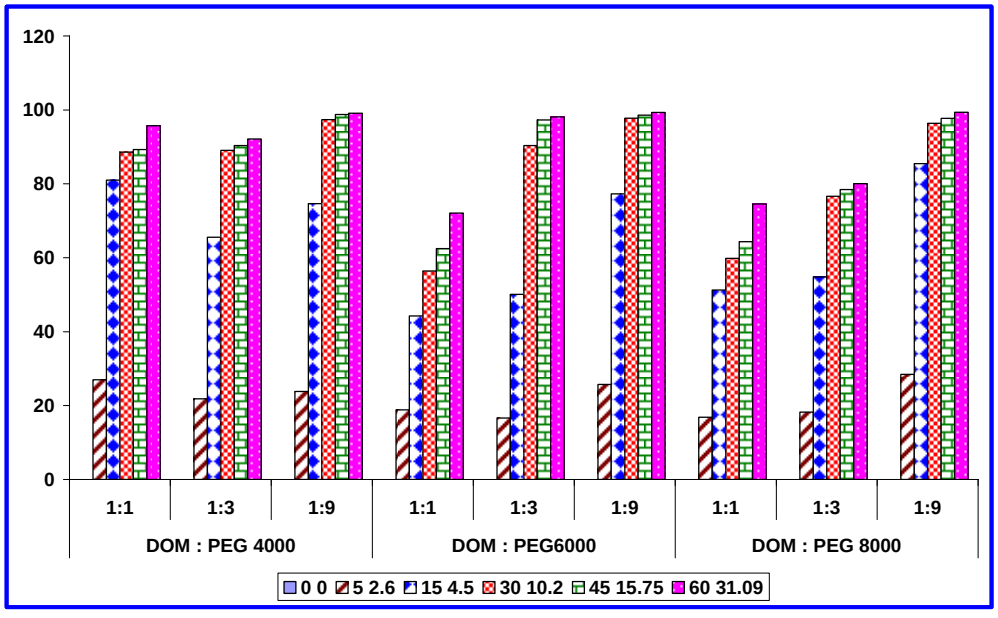


Figure 24: Dissolution profile of Domperidone from various solid dispersions

Table 13: Relation between % carrier and T_{50}, T_{90} values for Domperidone –PEG 4000 solid dispersions

% of drug	% of carrier	T_{50} (min)	T_{90} (min)
1	0	94.9	-
1	1	9.5	47.5
1	3	12.0	45.0
1	9	10.5	25.5

Table 14: Relation between % carrier and T_{50}, T_{90} values for Domperidone- PEG 6000 solid dispersions

% of drug	% of carrier	T_{50} (min)	T_{90} (min)
1	0	94.9	-
1	1	22.5	-
1	3	15.0	30
1	9	10.0	24.5

Table 15: Relation between % carrier and T_{50}, T_{90} values for Domperidone- PEG 8000 solid dispersions

% of drug	% of carrier	T_{50} (min)	T_{90} (min)
1	0	94.9	-
1	1	14.5	-
1	3	14.0	-
1	9	8.5	22.5

Table 16: Percentage Domperidone undissolved from pure form and from PEG 4000 solid dispersions at various drug carrier ratios

Time in minutes	percentage Domperidone undissolved from				
	Pure drug 10 mg	PM 1:1	1:1	1:3	1:9
0	100	100	100	100	100
5	97.22	83.67	73.00	78.17	95.15
15	91.59	50.92	18.95	34.44	85.36
30	84.90	26.20	11.38	10.96	2.61
45	75.04	25.67	10.71	9.63	1.24
60	68.91	21.63	4.23	7.85	0.88

Table 17: LOG Percentage Domperidone undissolved from pure form and from PEG 4000 solid dispersions at various drug carrier ratios

Time in minutes	Percentage domperidone undissolved from (log percentage undissolved)				
	Pure drug 10 mg	PM 1:1	1:1	1:3	1:9
0	2	2	2	2	2
5	1.9877	1.9225	1.8633	1.8930	1.9784
15	1.9618	1.7068	1.2776	1.5370	1.9312
30	1.9289	1.4183	1.0561	1.0398	0.4166
45	1.8752	1.4094	1.0297	0.9836	0.0934
60	1.8382	1.3350	0.6263	0.8948	0.055

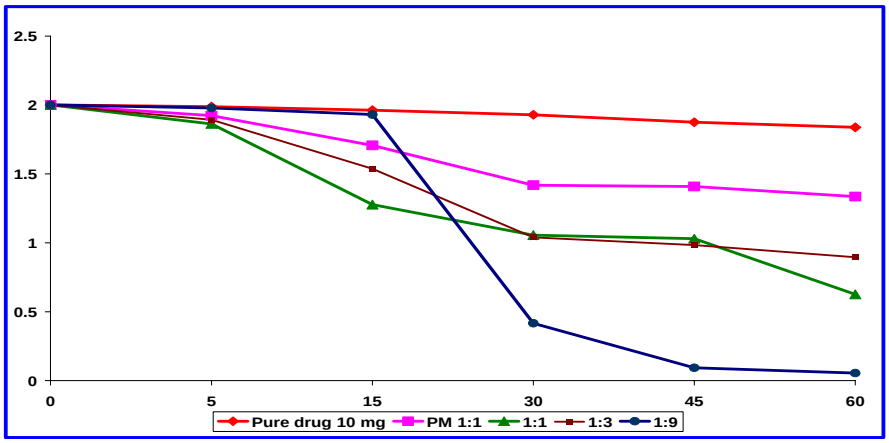


Figure 25: Percentage Domperidone undissolved from pure form and from PEG 4000 solid dispersions at various drug carrier ratios

Table 18: Percentage Domperidone undissolved from pure form and from PEG 6000 solid dispersions at various drug carrier ratios

Time in minutes	Percentage domperidone undissolved from				
	Pure drug 10 mg	PM 1:1	1:1	1:3	1:9
0	100	100	100	100	100
5	97.22	84.58	81.13	83.32	74.27
15	91.59	51.49	55.72	49.87	22.72
30	84.90	49.13	43.56	9.62	2.21
45	75.04	46.98	37.51	2.72	1.42
60	68.91	44.13	27.91	1.87	0.69

Table 19: LOG Percentage Domperidone undissolved from pure form and from PEG 6000 solid dispersions at various drug carrier ratios

Time in minutes	Percentage domperidone undissolved from (log percentage undissolved)				
	Pure drug 10 mg	PM 1:1	1:1	1:3	1:9
0	2	2	2	2	2
5	1.9877	1.9272	1.9091	1.9207	1.8708
15	1.9618	1.7117	1.7460	1.6978	1.3564
30	1.9289	1.6913	1.6390	0.9831	0.3443
45	1.8752	1.6719	1.5741	0.4345	0.1522
60	1.8382	1.6447	1.4457	0.2718	0.1611

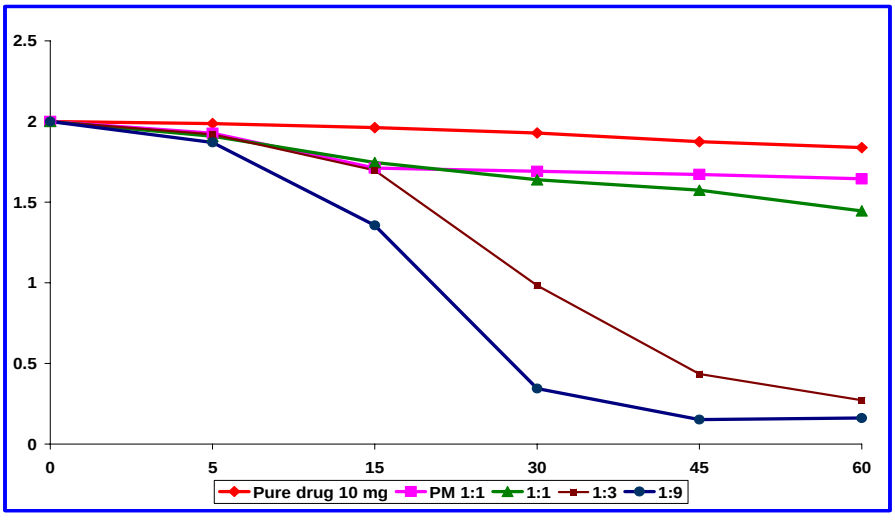


Figure 26: Percentage Domperidone undissolved from pure form and from PEG 6000 solid dispersions at various drug carrier ratios

Table 20: Percentage Domperidone undissolved from pure form and from PEG 8000 solid dispersions at various drug carrier ratios

Time in minutes	Percentage Domperidone undissolved from				
	Pure drug 10 mg	PM 1:1	1:1	1:3	1:9
0	100	100	100	100	100
5	97.22	86.32	83.18	81.73	71.52
15	91.59	52.33	48.71	45.18	14.52
30	84.90	47.05	40.13	23.32	3.64
45	75.04	41.17	35.62	21.52	2.26
60	68.91	37.51	25.44	19.94	0.64

Table 21: LOG Percentage Domperidone undissolved from pure form and from PEG 8000 solid dispersions at various drug carrier ratios

Time in minutes	Percentage Domperidone undissolved from (log percentage undissolved)				
	Pure drug 10 mg	PM 1:1	1:1	1:3	1:9
0	2	2	2	2	2
5	1.9877	1.9361	1.9200	1.9123	1.8544
15	1.9618	1.7187	1.6876	1.6549	1.1619
30	1.9289	1.6725	1.6034	1.3677	0.5611
45	1.8752	1.6145	1.5516	1.3328	0.3541
60	1.8382	1.5741	1.4055	1.2997	0.1938

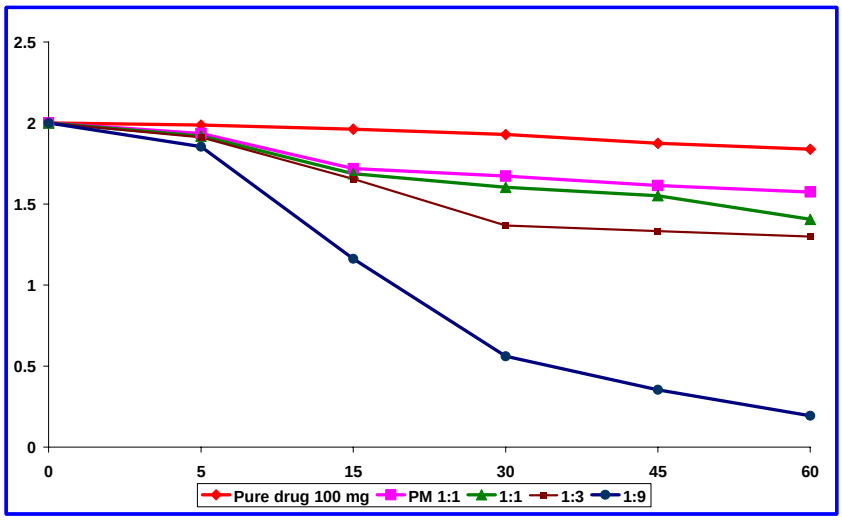


Figure 27: Percentage Domperidone undissolved from pure form and from PEG 8000 solid dispersions at various drug carrier ratios

Table 22: First order rate constant for Domperidone dissolution from various solid dispersions

Sample	K (min^{-1})
Pure drug	0.0046
DOM:PEG 4000	
PM	0.025
1:1	0.048
1:3	0.043
1:9	0.089
DOM: PEG 6000	
PM	0.011
1:1	0.018
1:3	0.071
1:9	0.078
DOM:PEG 8000	
PM	0.013
1:1	0.020
1:3	0.027
1:9	0.071

RESULTS AND DISCUSSION

Solid dispersion of Domperidone was prepared by depositing on the polymers namely PEG 4000, PEG 6000 and PEG 8000 by solvent evaporation method. Solid dispersions at drug: carrier ratios (1:1, 1:3, 1:9) were prepared and summarized in Table 6 .All solid dispersions prepared were found to be fine and free flowing powders. The percent of drug content in the solid dispersions were given in table .8. There was no significant loss of drug during the preparation of solid dispersions and the proportion of drug and carrier remained the same as that initially taken. The estimated drug content of the prepared solid dispersions was in the range of 100.95±1.4%.

The prepare solid dispersions were characterized by TLC, FTIR, X-ray diffraction and Differential Scanning Calorimetry

THIN LAYER CHROMATOGRAPHY

In TLC studies as per the data given in Table 7, Domperidone dispersed in various carriers showed the similar Rf (0.70) value as pure compound and no additional spots were detected. TLC studies thus indicated no interaction between Domperidone and carriers used in the solid dispersions. This observation also indicated that Domperidone was not decomposed during the preparation of solid dispersions.

FT-IR SPECTRAL ANALYSIS

Compatibility studies of Domperidone and the carriers PEG 4000(1:1, 1:3 and 1:9) were carried out by using FT-IR. The IR spectra obtained are given in Figure 4 - 8. The IR spectrum of Domperidone showed characteristic intense absorbance band at 3406.64 cm^{-1} (Aromatic C--H stretching), 1691.27 cm^{-1} (C=O stretching due to 5 member imides), 1485.88 cm^{-1}, 1590.99 cm^{-1} (C=C stretching), 760.78 cm^{-1} (mono substituted Benzene) and 1348 cm^{-1} (–NH stretching).

PEG 4000 shown characteristic vibrations at 2881.13 cm^{-1} (C—H stretching in $CH_{2)}$, 1110.8 cm^{-1} (C—O stretching due to ether$_{)}$, 3699.76 cm^{-1} (O--H stretching due to free OH group$_{)}$.

IR spectra of Domperidone solid dispersions at 1:1, 1:3 and 1:9 showed insignificant shifts in peaks for both Domperidone and PEG 4000, suggesting the absence of interaction between Domperidone and PEG 4000.

POWDER X- RAY DIFFRACTION

The presence of numerous distinct peaks in the X-ray diffraction spectrum indicate that Domperidone was present as a crystalline material with distinct intense diffraction peaks appearing at a diffraction angle of 2θ at 4.93^{o},9.56^{o},14.29^{o},15.85^{o}, also less intense peaks at 25.10^{o},29.31^{o} and 31.75^{o}. PEG 4000 exhibited a distinct pattern with diffraction peaks at angle 2θ at 19.41^{o} and 23.47^{o}, Figure 9-12.

Solid dispersion systems showed fewer, broader, and less intense peaks when compared to that of pure drug. When PEG 4000 content was increased from 50 % (1:1 SD) to 90 % (1:9 SD), some characteristic peaks of Domperidone (25.10^{o}, 29.31^{o}) were disappeared. The position of PEG 4000 patterns in SD systems were the same as super imposable which ruled out the possibility of chemical interaction between Domperidone and PEG 4000. These results suggest that Domperidone was dispersed

homogenously in an amorphous state or dissolved into PEG 4000 **Lin CW and Cham TM, 1996**.

DIFFERENTIAL SCANNING CALORIMETRY

The DSC details were given in Figure 13 - 17. The DSC curve of pure Domperidone exhibited a single endothermic response corresponding to the melting point of the drug. Onset of melting was observed at 249.5^{o} C. All Domperidone PEG 4000(1:1, 1:3 and 1:9) solid dispersions showed, a constant melting at approximately 55.8^{o} C corresponding to the melting point of PEG 4000 .The presence of DOM in the SDs hardly affected the melting point of PEG 4000, but a small amount of PEG 4000 caused depression of melting point of Domperidone.

Solid dispersions exhibited two endothermic transitions corresponding to the melting of the polymer and of the drug. These similarities suggest the absence of chemical interaction between both species. The melting point of Domperidone in the SDs decreased as the concentration of polymer increases from 234.3^{o} C (50 %) to 176.8^{o} C (90%) and shifted to the lower melting point. This shows that the transition of Domperidone from lower energy crystalline state to higher energy amorphous state.

SCANNING ELECTRON MICROSCOPY

The scanning electron microscopy was carried out and photos were taken for the pure DOM and DOM-PEG 4000(1:1) solid dispersion, photos were given in Figure 18 &19. The SEM photos revealed that there was a morphological change of pure Domperidone from crystalline nature to amorphous nature in the solid dispersion.

DISSOLUTION STUDIES

The dissolution profiles of pure drug, physical mixture and various solid dispersions were given in Table 9-12 and Figure 21-24. The time required to dissolve 50% of the drug T_{50} was taken as a basis for comparison of the dissolution rate. It was evident that the rate of dissolution of pure Domperidone was very slow, only 50 % of the drug was dissolved after 1.5 hr. T_{50} values decreased from 1.5 hr for the pure drug to less than 15 min for DOM-PEG 4000 solid dispersions. First order rate constant “K” values found to be increased when the carrier concentration was raised indicating the fast dissolution of Domperidone at higher carrier concentration The increased dissolution rate from SDs can be attributed to the lack of crystallinity and increased wettability .

Dissolution rate of Domperidone from its physical mixture containing 50 % w/w of Domperidone was significantly higher than for the pure drug. T_{50} value was reached after 35 min for the PM. Dry mixing brings the drug in close contact with the hydrophilic polymer and the increased dissolution rate can thus be explained as a result of increased wettability and dispersibility of Domperidone. Indeed, during dissolution experiments, it was noticed that physical mixtures immediately sink to the bottom of the dissolution vessel as solid dispersions do, whereas the pure drug floats for a longer period on the surface of the dissolution medium.

Among the solid dispersions prepared DOM-PEG 4000(1:9), DOM-PEG 6000(1:9) and DOM-PEG 8000(1:9) gave the highest dissolution rate. SDs of DOM- PEG 4000(1:1, 1:3 and 1:9) gave dissolution rate more than 90% at 45 min when compared to other SDs. The rate of dissolution of SDs showed 3 fold increase when compared to pure drug.

The order of dissolution of Domperidone from various carriers was DOM-PEG 8000(1:9) > DOM-PEG 6000(1:9) > DOM-PEG 4000(1:9) > DOM-PEG 6000(1:3) > DOM-PEG 4000(1:1) > DOM-PEG 4000(1:3) > DOM-PEG 8000(1:3), DOM-PEG 8000(1:1)> DOM-PEG 6000(1:1) > pure drug.

FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF SELECTED DOMPERIDONE SOLID DISPERSION

Domperidone a prokinetic dopamine receptor antagonist indicated for the treatment of nausea and vomiting as well as in chemotherapy induced nausea and vomiting. As the oral bioavailability of Domperidone is only 13% to 17 % due poor aqueous solubility and hepatic first pass metabolism, attempts were made to improve bioavailability by formulating Orodispersible tablets of selected solid dispersions using non sugar muco adhesive sweetener (NSMAS) for imparting good mouth feel and thus compliance. ODTs can improve bioavailability of drugs undergoing hepatic metabolism by facilitating drug for presystemic absorption and also by bypassing hepatic first pass effect.

PREPARATION OF NON SUGAR MUCOADHESIVE SWEETENER (NSMAS)

Carbomer was dispersed in 20 ml of water. Then aspartame was granulated with Carbomer solution and dried at 40^{o} C. Sift through 60 mesh sieve [singh et al., 2006].

Table 23: Formula of Non Sugar Mucoadhesive Sweetener (NSMAS)

S.No	Ingredients	Amount
1	Aspartame	20 gm
2	Carbomer	0.4 gm
3	Water	20 ml

Formulation of Orodispersible tablets

Domperidone solid dispersion in PEG 4000 at a drug carrier ratio of 1:1, 1:3 and 1:9 were formulated into tablets using directly compressible mannitol as diluent and crosscarmellose sodium as superdisintegrant in 2%, 4% as well as 8% with other additives and evaluated for drug release characteristics. Tablets containing solid dispersion equivalent to 10 mg of Domperidone were prepared using various additives given in Table 24.

Table 24: Formula of Domperidone Orodispersible tablets

S. No	Ingredients	Formulations (mgs)								
		F1	F2	F3	F3	F4	F5	F7	F8	F9
1	Domperidone: PEG 4000(1:1) drug carrier ratio.	20	20	20						
2	Domperidone: PEG 4000(1:3) drug carrier ratio.				40	40	40			
3	Domperidone: PEG 4000(1:9) drug carrier ratio.							100	100	100
5	Directly compressible mannitol	168	164	156	148	144	136	88	84	76
6	Croscarmellose sodium	4	8	16	4	8	16	4	8	16
7	Magnesium stearate	2	2	2	2	2	2	2	2	2
8	Talc	2	2	2	2	2	2	2	2	2
9	Non sugar mucoadhesive sweetener(NSMAS)	4	4	4	4	4	4	4	4	4

Table 25: Materials used for tablet formulation

Name of the materials	Name of company
Domperidone: PEG 4000 (1:1, 1:3, 1:9) drug carrier ratio	Prepared in previous chapter
Domperidone	Carewell pharma, Chennai
Directly compressible mannitol	IPCA Ltd, Mumbai.
Croscarmellose sodium	Maple biotech pvt Ltd
Talc	Himedia Laboratories Pvt Ltd
Aspartame	Himedia Laboratories Pvt Ltd
Cellulose acetate phthalate	Fluka analytical
Magnesium stearate	SD Fine chemicals Ltd, Mumbai.

Table 26: Equipments used for tablet formulation

Name of equipment	Name of company
Tablet punching machine	Rimek Mini Press 1
Tablet disintegration test apparatus	Remi equipments
Pfizer tablet hardness tester	Scientific engineering corporation
Roche friability tester	Remi equipments
Dissolution apparatus	Labindia Disso 2000
UV spectrometer	Jasco V 530
pH tester 1 (water proof)	Oakton instruments.

Method

The required amount of drug and the other additives were mixed thoroughly in a mortar and the tablets are prepared by direct compression using Rimek Mini Press 1 punching machine. The prepared tablets were stored in screw capped glass bottles. The prepared tablets were evaluated for various quality control and compatibility studies.

EVALUATION OF ORODISPERSIBLE TABLETS

The formulated tablets were subjected for the following compatibility studies and quality control tests.

Compatibility studies

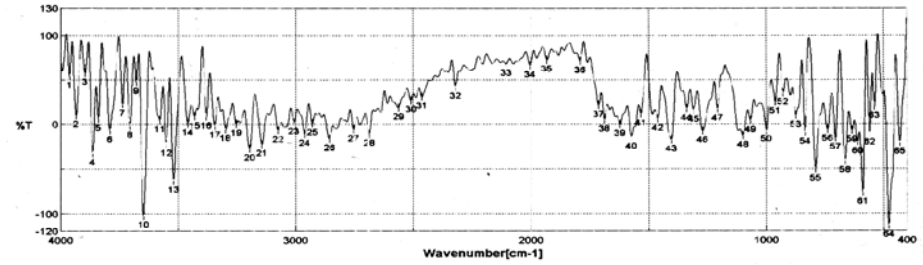
- FTIR compatibility study
- TLC study

Quality control tests

- Thickness and diameter
- Weight variation
- Disintegration test
- Friability
- Hardness
- Drug content uniformity
- Dissolution
- Stability studies

FTIR compatibility study

Fourier Transform (FTIR) spectra of formulated ODT was obtained in the range of 400-4000 cm^{-1} using a Jasco-FT-IR 8201 PC Spectrophotometer (Jasco.Essex) by the KBr disc method. The IR Spectra obtained was given in Figure 28.



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	64	Scanning Speed	2 mm/sec
Date/Time	12/1/2008 4:04PM	Update	12/8/2008 11:57AM
Operator	C.Geetha		
File Name	TAB 4000		
Sample Name	TAB 4000		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3983	54.3665	2	3935.04	10.2279	3	3897.43	57.9078	4	3864.65	-32.6483	5	3846.54	6.32849
6	3792.33	-6.68448	7	3738.33	22.8274	8	3705.55	-1.67404	9	3678.56	47.5407	10	3647.7	-102.238
11	3578.27	4.76548	12	3551.27	-22.4601	13	3520.42	-63.2713	14	3460.63	1.02333	15	3431.71	8.64398
16	3381.57	8.58229	17	3345.89	-1.66556	18	3299.61	-5.46566	19	3254.29	0.75382	20	3196.43	-27.3483
21	3144.37	-22.3067	22	3075.9	-6.579	23	3008.41	2.41121	24	2962.13	-10.8838	25	2930.31	1.20173
26	2857.02	-16.3752	27	2753.85	-5.67727	28	2698.28	-11.1313	29	2563.9	18.7388	30	2506.9	26.7287
31	2462.65	31.0431	32	2320.91	42.3717	33	2105.89	68.1526	34	2002.71	66.4586	35	1931.36	72.5501
36	1790.58	71.4649	37	1712.48	21.2373	38	1687.41	5.46043	39	1620.88	0.00443486	40	1572.66	-14.5531
41	1532.17	11.7451	42	1461.78	8.17478	43	1403.92	-17.6186	44	1338.36	17.745	45	1306.43	15.7778
46	1270.86	-7.43596	47	1206.26	17.0662	48	1098.26	-12.7109	49	1066.44	4.43446	50	998.946	-6.49594
51	961.341	25.2684	52	927.593	35.4568	53	873.596	9.98475	54	834.062	-9.10284	55	788.743	-50.8615
56	737.639	-5.96578	57	704.855	-15.6938	58	664.357	-41.2664	59	635.43	-6.99704	60	611.324	-20.0807

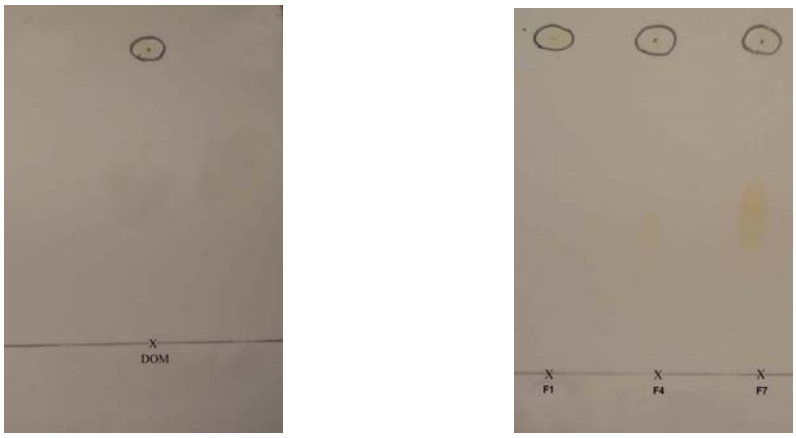
Figure 28: FTIR spectrum of formulated Domperidone ODT (F1)

Thin layer chromatography

Thin layer chromatographic method was carried out to study the interaction between the drug and carriers and to confirm the stability of the ODTs prepared. For this, the pure drug and the formulations (F1, F4 and F7) were subjected to chromatographic studies. Chromatograms were generated using precoated TLC plates as stationary phase and methanol: dioxin: ammonium acetate solution (40:40:20 %v/v) as mobile phase. The Rf values obtained were given in Table 27, the chromatograms were given in Figure 29.

Table 27: TLC data for various formulated ODTs

S.No	Formulation	Rf value	No of spots
1	Pure drug	0.70	single
2	F1	0.71	single
3	F4	0.71	single
4	F7	0.70	single



Pure Domperidone **ODT Formulations**

Figure 29: Thin layer chromatogram of drug and formulated ODTs

Thickness and diameter

Uniform compression force and volume of die fill, leads to uniform thickness. From each batch three ODTs were taken and checked with vernier, the mean of three tablets and standard deviation were calculated and the results were given in the Table 29. Similarly three tablets were taken and checked for diameter using vernier, the results were given in Table 29.

Weight variation test

Twenty tablets were taken weighed individually as per BP. They were evaluated for the weight variations. The weight variation allowed as per BP limit is 7.5%. The weight of individual tablets were within the BP limits. The results were shown in Table 28.

Pharmaceutical form	Average mass	% Deviation
Tablets	≤ 80 mg	± 10
	> 80 mg <250 mg	± 7.5
	≥ 250 mg	± 5

$$\text{\% Deviation} = \frac{\text{average weight - individual weight}}{\text{Average weight}} X\ 100$$

Table No. 28: Weight variation of formulated Domperidone ODTs

S.No	Formulation code	Weight range of 20 ODTs	Average weight	Limit range (±7.5%)
1	MS	185-211	198.41	183.53-213.29
2	F1	198-212	208.36	192.76-223.96
3	F2	183-208	195.21	180.57-209.85
4	F3	186-215	197.48	182.66-212.29
5	F4	197-225	209.47	193.76-225.18
6	F5	188-214	201.63	186.51-216.75
7	F6	184-210	198.42	183.54-213.30
8	F7	194-217	203.91	188.62-219.20
9	F8	188-207	196.35	181.63-211.07
10	F9	189-211	197.49	182.68-212.30

n = 3,± Sd

Disintegration test

The USP device to test disintegration uses six glass tubes that are three inches long open at the top and held against 10 inch screen at the basket rack assembly. A tablet is placed in each tube and the basket is positioned in a 1 liter beaker of distilled water at 37±2°C, such that the tablets below the surface of the liquid on their movement and descend not closer than 2.5 cm from the bottom of the tester. The results were shown in Table 29 and Figure 30.

Friability test

Friability test was performed on the formulated tablets. The weight of the tablets after undergoing 100 revolutions was found to be within the limits 0.5 to 1.0%. The results were shown in Table 29.

Hardness

Pfizer hardness tester was used for measuring the hardness of formulated Domperidone ODTs. Five tablets wee taken randomly and subjected to test. The hardness was found to be 4-5.4 kg/cm^2. The results were shown in Table 29.

Table No 29: Hardness, friability, and disintegration time of formulated Domperidone ODTs and marketed sample

S. No	Formulation code	Thickness (mm)	Diameter (mm)	Hardness (Kg/Cm^2)	Friability (%)	Disintegration time (sec)
1	F1	3.1±0.2	7.0±0.6	4.2±0.16	0.55	171±2.86
2	F2	3.0±0.1	7.1±0.8	4.1±0.11	0.62	78±1.21
3	F3	3.2±0.2	7.2±0.8	4.1±0.13	0.68	73±1.05
4	F4	3.0±0.2	7.0±0.9	4.3±0.08	0.52	480±3.22
5	F5	3.0±0.1	7.2±0.5	4.8±0.15	0.55	436±2.66
6	F6	3.1±0.3	7.0±0.7	4.9±0.12	0.61	321±2.32
7	F7	3.1±0.2	7.0±0.6	5.4±0.18	0.54	511±2.57
8	F8	3.1±0.1	7.1±0.9	5.2±0.17	0.57	494±2.54
9	F9	3.0±0.2	7.1±0.8	5.2±0.12	0.50	487±2.43
10	MS	3.0±0.3	7.0±0.6	5.4±0.16	0.54	294±1.38

n = 3, ± Sd.

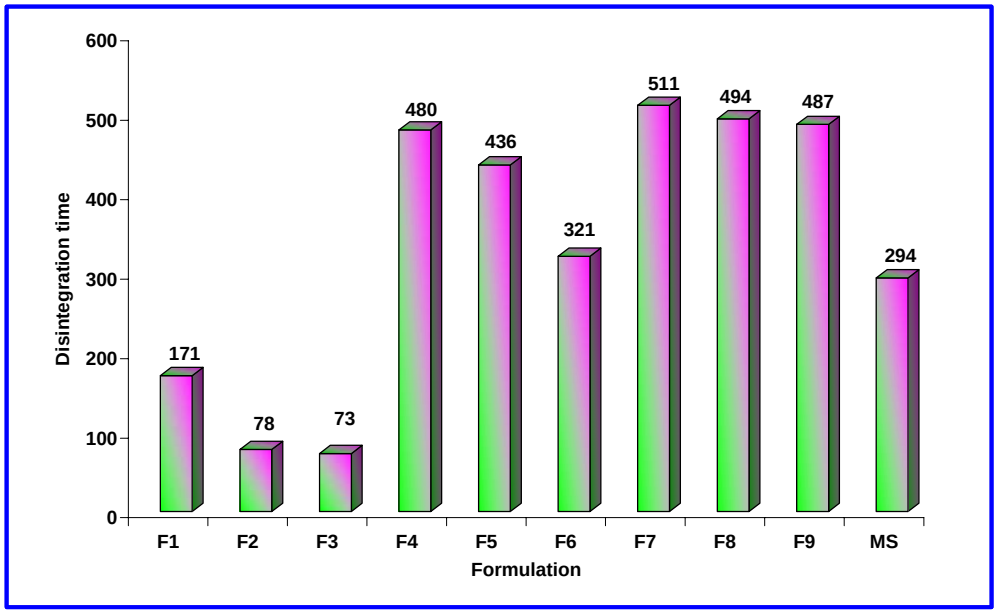


Figure 30: Disintegration time of formulated Domperidone ODTs and marketed sample

Drug content uniformity

The prepared tablets containing Domperidone solid dispersion was tested for drug content uniformity. Tablets were dissolved in 100 ml of 0.1 M HCl in 100 ml volumetric flask which was previously clean and dry. This solution after suitable dilution was measured for absorbance at 286 nm in a Jasco V530 UV visible spectrophotometer. The results were shown in Table 30.

Table No. 30: Drug content uniformity of formulated Domperidone ODTs

S.No	Formulation code	Amount of Domperidone per ODT	
		Amount in milligram	Amount in %
1	F1	10.07±0.05	100.73±0.05
2	F2	10.18±0.11	101.82±0.11
3	F3	9.88±0.08	98.86±0.08
4	F4	10.48±0.06	104.85±0.06
5	F5	10.39±0.10	103.91±0.10
6	F6	10.11±0.06	101.19±0.06
7	F7	10.27±0.09	102.74±0.09
8	F8	10.21±0.11	102.17±0.11
9	F9	10.24±0.06	102.46±0.06
10	MS	10.15±0.03	101.52±0.03

n=3, ± Sd.

***In-vitro* Dissolution studies**

Dissolution of Domperidone from formulated ODTs were studied in BP dissolution medium. The formulated tablets containing solid dispersions equivalent to 10mg of Domperidone were taken and the paddle type stirrer was adjusted to 50 rpm. The temperature was maintained at 37±1°C. 5 ml aliquot dissolution media was withdrawn at different time intervals and volume withdrawn was replaced with fresh quantity of dissolution media. The samples were analyzed for Domperidone by measuring absorbance at 286 nm using Jasco UV visible spectrometer. 0.1 M HCl was used as blank. The percentage of Domperidone dissolved at various time intervals was calculated and plotted against time. The results are shown in Table 31-34 and Figure 29-32.

Table 31: Dissolution profile of formulated ODTs of DOM- PEG 4000 (1:1) solid dispersions

Time in minutes	Percentage of Domperidone release in 0.1 M HCl			
	Marketed sample (MS)	F1	F2	F3
0	0	0	0	0
5	42.77±1.80	66.15±1.84	82.74±0.92	80.27±0.54
15	83.94±1.52	84.32±1.19	92.77±0.94	92.42±1.32
30	86.51±1.48	86.54±1.12	93.06±1.13	92.53±1.47
45	87.91±1.69	90.41±0.98	94.25±1.25	93.44±1.65
60	88.62±1.37	91.36±1.04	94.89±1.08	95.66±1.55

n=3, ± Sd

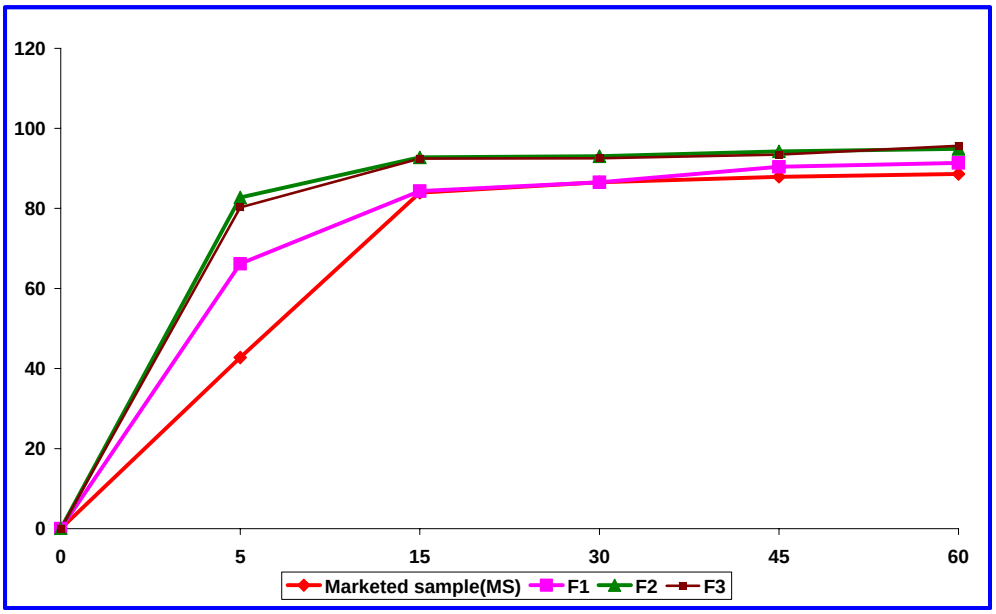


Figure 31: Dissolution profile of formulated ODTs of DOM- PEG 4000 (1:1) solid dispersions

Table 32: Dissolution profile of formulated ODTs of DOM- PEG 4000 (1:3) solid dispersions

Time in minutes	Percentage of Domperidone release in 0.1 M HCl			
	Marketed sample (MS)	F4	F5	F6
0	0	0	0	0
5	42.77±1.80	50.94±1.09	33.27±0.98	52.85±2.12
15	83.94±1.52	93.27±1.16	81.47±1.01	95.77±1.05
30	86.51±1.48	96.05±1.75	98.27±1.54	96.05±1.16
45	87.91±1.69	97.03±0.80	98.34±1.14	97.67±1.75
60	88.62±1.37	99.22±1.01	99.39±1.55	98.20±0.85

n=3, ± Sd

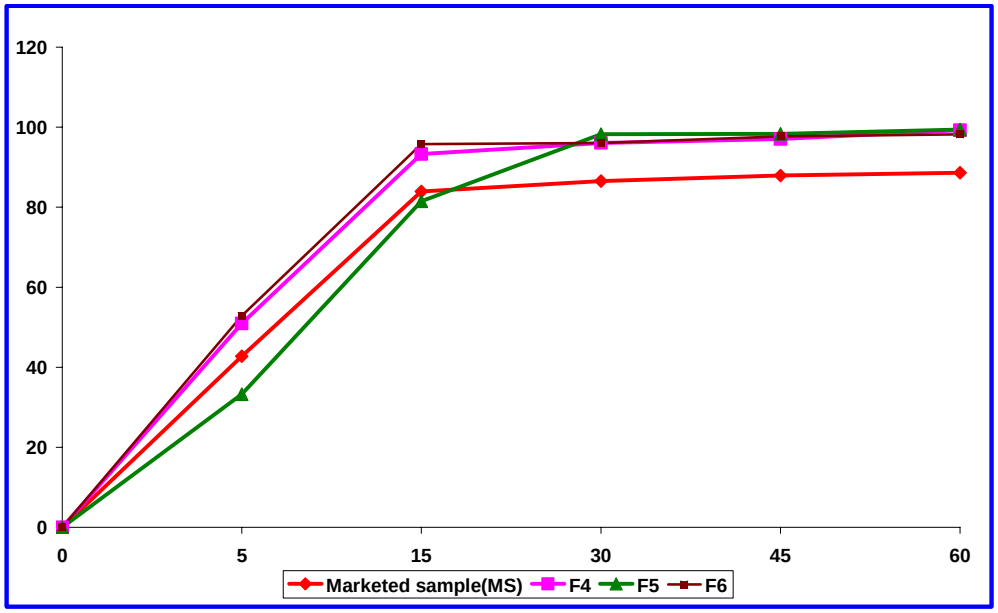


Figure 32: Dissolution profile of formulated ODTs of DOM- PEG 4000 (1:3) solid dispersions

Table 33: Dissolution profile of formulated ODTs of DOM- PEG 4000 (1:9) solid dispersions

Time in minutes	Percentage of Domperidone release in 0.1 M HCl			
	Marketed sample (MS)	F7	F8	F9
0	0	0	0	0
5	42.77±1.80	29.18±0.61	29.71±2.14	27.42±2.13
15	83.94±1.52	83.02±10.2	78.37±1.35	74.04±1.63
30	86.51±1.48	98.20±1.07	91.29±1.79	88.69±1.51
45	87.91±1.69	101.26±1.82	93.30±0.83	90.20±0.78
60	88.62±1.37	101.29±0.89	93.65±1.36	92.39±0.57

n=3, ± Sd

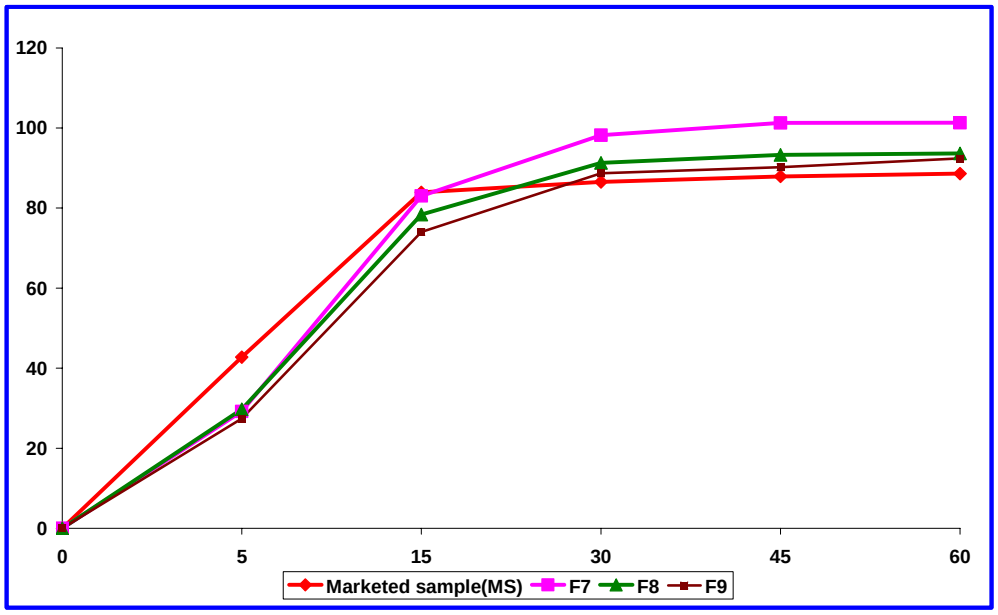


Figure 33: Dissolution profile of formulated ODTs of DOM- PEG 4000 (1:9) solid dispersions

Table 34: Dissolution profile of formulated Domperidone ODTs and marketed sample

Time in minutes	Percentage of Domperidone released from									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	Marketed sample
0	0	0	0	0	0	0	0	0	0	0
5	66.15	82.74	80.27	50.94	33.27	52.85	29.18	29.71	27.42	42.77
15	84.32	92.77	92.42	93.27	81.47	95.77	83.02	78.37	74.04	83.94
30	86.54	93.06	92.53	96.05	98.27	96.05	98.20	91.29	88.69	86.51
45	90.41	94.25	93.44	97.03	98.34	97.67	101.26	93.30	90.20	87.91
60	91.36	94.89	95.66	99.22	99.39	98.20	101.29	93.65	92.39	88.62

n=3, ± Sd

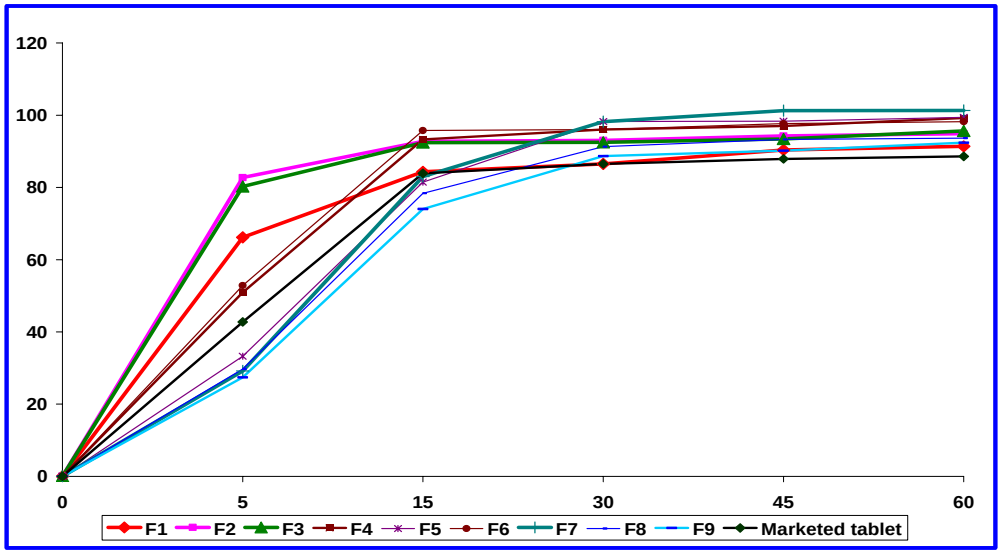


Figure 34: Dissolution profile of formulated Domperidone ODTs and marketed sample

Stability studies

The purpose of stability testing is to investigate how the quality of a drug product changes with time under the influence of environmental factors such as temperature, humidity and light and to establish a shelf life for the product and to recommend storage conditions. The guidelines promulgated by the international conference on Hormonisation (ICH) are the most commonly accepted one for the stability studies.

Among all formulated ODTs, formulation F3 was selected for the real time stability study based on its disintegration and dissolution rate profile in 0.1 M HCl, and it was kept in the real time stability chamber (30^{o} C and 70% RH) for stability studies. After specified period of time, the samples were collected and evaluated for hardness, friability, disintegration time and percentage of drug release. The results were given in the Table 35 -36 and Figure 35.

Table 35: Physical parameters of stability formulation (F3) in real time stability study

S.No	Parameters	Initial/zero Month	Real time stability study	
			1'st month	2'nd month
1	Hardness (kg/cm^2)	4.1±0.13	4.1±0.10	4.1±0.12
2	Friability (%w/w)	0.68	0.67	0.66
3	Disintegration time (sec)	73±1.05	72±1.2	72±1.0

n=3, ± Sd

Table 36: Dissolution profile of stability formulation (F3) in real time stability study

Time in mins	% of drug release		
	Initial/zero month	1'st month	2'nd month
0	0	0	0
5	80.27±0.54	78.85±0.82	77.22±1.84
15	92.42±1.32	90.10±1.74	88.68±1.19
30	92.53±1.47	91.56±1.44	90.78±1.11
45	93.44±1.65	92.06±1.30	91.64±0.98
60	95.66±1.55	95.12±1.16	95.08±1.04

n=3, ± Sd

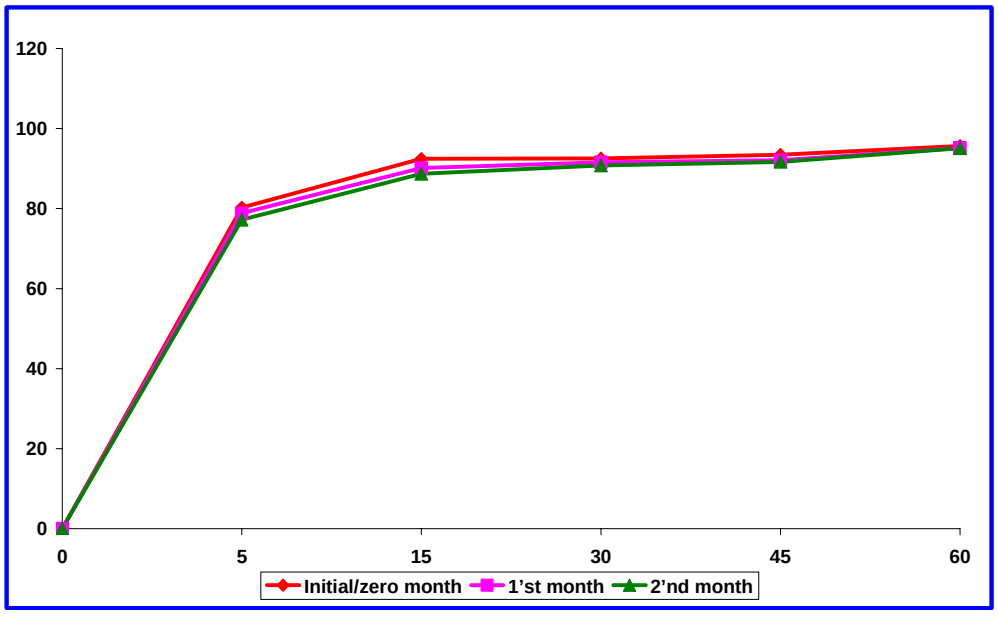


Figure 35: Dissolution profile of stability formulation (F3) in real time stability study

MARKETING STRATEGY

The total market share of Domperidone tablets, according to the Ac-Nielson ORG -2008 data was about 39.5 crore. This market can be further expanded by introducing brand extensions catering to the need of the prescriber and the patient. The prepared ODTs address the issues of poor oral bioavailability of Domperidone and offer a pleasant mouth feel dispersible dosage form to improve the patient compliance especially geriatric and pediatric patients undergoing treatment for chemotherapy induced nausea and vomiting.

Strategic target customers

The marketing strategy is primarily targeted to the following customers

- Prescribers of immediate release Domperidone tablets.
- Prescribers of metoclopramide.
- Oncologists who treat CINV.
- Pediatricians who practice pediatric oncology.
- General prescribers treating nausea and vomiting.

Proposed promotional strategy

- To highlight the superiority of ODTs containing SDs in improving oral bioavailability in comparision to immediate release tablets.
- The advantage of Domperidone over Metoclopramide in terms of CNS side effects, as DOM does not cause significant CNS side effects.
- To highlight the use of DOM in CINV for geriatric and pediatric patients.
- To highlight the NSMAS and disintegration time and pleasant mouth feel for better patient compliance.

RESULTS AND DISCUSSION

An attempt was made to formulate Domperidone Orodispersible tablets containing Domperidone solid dispersion with hydrophilic polymer PEG to improve oral bioavailability, patient compliance and markettability. Nine batches of Domperidone ODTs were prepared using DOM-PEG 4000 SDs (1:1, 1:3 and 1:9) with croscarmellose sodium in the concentration 2%, 4% and 8% respectively by direct compression method. Directly compressible mannitol, talc, magnesium stearate and Non sugar mucoadhesive sweetener (NSMAS) made with aspartame were used as a excipients for the formulation and the details were shown in Table 24.

Compatibility studies

The compatibility between the drug and the excipients were evaluated by FTIR matching approach. The IR spectra of F1 showed in Figure 28 shown a characteristic absorbance peaks at 3431.71 cm^{-1}, 1687.41 cm^{-1} , 1572.66 cm^{-1}, 1461.78 cm^{-1}, 1338.36 cm^{-1} and 788.74 cm^{-1} these frequencies matched with frequencies observed in the IR spectrum of pure Domperidone. This confirmed that the absence of any chemical interaction between Domperidone and excipients.

The TLC data was shown in Figure 29, revealed that the Rf value of F1, F4 and F7 were matching with that of pure DOM and no additional spots were seen. This suggested that there were no interaction between the drug and the excipients.

Physical characterization

The diameter, thickness and friability of all formulated ODTs were given in Table 29. Hardness was found to be in the range of 4.1±0.11 to 5.4±0.18, and was satisfactory. The percentage weight loss in the friability test was found to be between 0.50 % to 0.68 % and was less than 1% in all formulations indicated that tablets had good mechanical resistance.

Weight variation and Drug content uniformity

To be acceptable by USP standards, the weight variation tolerance for uncoated tablets must be 7.5% or less. As the tablet powder mixture was free flowing, tablets produced were of uniform weight with acceptable weight variation due to uniform die fill .All the ODTs prepared were found to contain the medicament within 102.1± 1.65 % of label claim. All the formulated ODTs (F1-F9) employing super disintegrant Croscarmellose sodium were found to be good quality fulfilling the official requirements of compressed tablets for weight variation and content uniformity, Table 28 and 30.

Disintegraton test

The disintegration profile was given in Table 29 and Figure 30 showed among all formulations F1, F2 and F3 ODTs disintegrated within 3 minutess, and fulfilling the BP requirement for ODTs. Formulation F3 containing 8% of croscarmellose sodium had faster disintegration time than F1 and F2 (2% and 4% respectively). The disintegration time of formulations F1, F2 and F3 were faster than the marketed sample of immediate release conventional tablet .

In ODTs of SDs containing 50 % (F1, F2 and F3) and 75% (F3, F4 and F6) of PEG 4000, as the concentration of croscarmellose sodium increases disintegration time decreases exponentially. But ODTs of SDs containing 90% of PEG 4000(F7, F8 and F9) the disinegration time was almost similar (511 ±2.5 sec, 494±2.5 sec and 487±2.4 sec) as the concentration of croscarmellose sodium increased. The increased disintegration time of tablets may be due to large amount of PEG 4000. When there was a large amount of PEG 4000, its binding properties were stronger than the swelling and disintegrating effect of croscarmellose sodium, slowing disintegration time.

In contrast, when there was a small amount of PEG 4000 (F1, F2 and F3) the effect of croscarmellose sodium was more pronounced, allowing faster disintegration. The order of disintegration was found to be F3 < F2 < F1 < MS< F6 < F5 < F4 < F9 < F8 < F7.

Dissolution studies

The dissolution profile of formulated ODTs and conventional marketed formulation were shown in Table 31 - 34. Tablets formulated with solid dispersions gave rapid dissolution of the medicament when compared to that of marketed sample. The dissolution of medicament from all tablets followed first order kinetics. The percentage release of all formulations (F1-F9) was between 90 and 101 % at 45 min when compared with the marketed sample which had around 89% release.T_{90} was less than 15 min for formulations F2,F3,F4 and F6, but for marketed sample t_{90} is more than 60 minutes. This shows faster release of drug from ODTs when compared to market sample. The faster and increased rate of release may be due to the rapid disintegration and increased wetability because of the hydrophilic polymer.

The order of dissolution of Domperidone from various ODT formulations was F7 > F5 > F4 > F6 > F3 > F2 > F8 > F9 > F1 > MS .

Stability studies

Data for stability studies were given in Table 35 and 36 shown that the stability studies performed for F3 at temperature 30^{o} C and relative humidity of 70 % revealed that no considerable changes were observed in drug content during 2 months.

Marketing strategy

Based on the market potential of Domperidone ODTs , the strategy focused on the merits of Domperidone over Metoclopramide in treating nausea and vomiting, the advantage of ODTs over immediate release tablets in terms of compliance, the advantage of improved bioavailability due to the formulation containing solid dispersion of Domperidone and also its release in the oropharangeal region which by pass hepatic first pass effect.

SUMMARY AND CONCLUSION

Studies were under taken on the formulation and evaluation of Orodispersible tablets of Domperidone from selected solid dispersions with hydrophilic polymer PEG with a view to improve dissolution as well as oral bioavailability, patient compliance marketability characteristics of Domperidone. Three grades of polyethylene glycols viz PEG 4000, PEG 6000 and PEG 8000 were used to prepare the SDs of Domperidone by solvent evaporation method at various drugs: carrier ratios namely (1:1, 1:3 and 1:9). The SDs prepared was found to be fine and free flowing powders.

Interaction studies such as TLC, FTIR revealed no interaction between drug and polymer PEG.

X-ray diffraction studies revealed that crystalline nature of Domperidone in pure form was reduced to amorphous form in the dispersions. The thermal behavior of Domperidone-PEG SDs (1:1, 1:3 and 1:9) was studied using DSC showed shifting of endothermic peaks of Domperidone to lower melting point, indicating transition of low energy crystalline nature of Domperidone in pure form to a higher energy amorphous state. Endothermic peaks pertaining to the polymer has not shown any change, this revealed that DOM has completely homogenously dispersed in the polymer and shown no interaction.

The SEM of pure drug and the solid dispersion revealed that the changes in the morphological characteristics of pure Domperidone from crystalline nature to amorphous nature in the solid dispersion.

Results of dissolution studies showed rapid and fast dissolution of Domperidone from all solid dispersions when compared with the pure drug and physical mixture. Good correlation was observed between percentage carrier in the solid dispersion and T_{50} and T_{90} values. The higher dissolution rate was observed with drug: carrier ratio of 1:9. SDs of PEG 4000 at 1:1, 1:3 and 1:9 gave more than 90 % release at 45 min.

The order of dissolution of Domperidone from various carriers is DOM-PEG 8000(1:9) > DOM-PEG 6000(1:9) > DOM-PEG 4000(1:9) > DOM-PEG 6000(1:3) > DOM-PEG 4000(1:1) > DOM-PEG 4000(1:3) > DOM-PEG 8000(1:3), DOM-PEG 8000(1:1) > DOM-PEG 6000(1:1) > pure drug.

Domperidone solid dispersion in PEG 4000 (1; 1, 1:3 and 1:9) was formulated into tablets with superdisintegrant croscarmellose sodium in (2%,4% and 8%), directly compressible mannitol as diluents and non sugar mucoadhesive sweetener and other additives.

Compatibility studies by FTIR and TLC revealed absence of any chemical interaction between Domperidone and excipients.

Quality control tests such as friability, hardness weight variation and content uniformity showed all ODTs fulfilled the official requirement of compressed tablets.

ODTs prepared with DOM- PEG 4000(1:1), F1,F2 and F3 showed disintegration time less than 3 min when compared with the marketed sample which took almost 5 minutes and also fulfilled BP requirement for ODTs. Other formulations (F4, F5, F6, F7, F8 and F9) showed DT more than 3 min and were not fulfilled the requirements, thus cannot be considered as ODTs.

The dissolution of Domperidone from ODTs was found to be fast and rapid when compared with marketed sample. The additives added have not hindered the dissolution of Domperidone from SDs. All ODT formulations based on the solid dispersion fulfilled the official dissolution requirements. The stability studies revealed that there were no considerable differences in drug content and dissolution profile over a period of two months.

Since it can be concluded that formulations F1,F2 and F3 were formulated using DOM-PEG 4000 (1:1) with superdisintegrant croscarmellose sodium in 2%,4% and 8% respectively, were adhere to the BP requirements in terms of disintegration time and dissolution profile to be considered as Orodispersible Tablets of Domperidone.

As other formulations namely F4, F5, F6, F7, F8, and F9 were shown disintegration time more than 3 minutes thus cannot be considered as Orodispersible tablets as per BP requirements.

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ABBREVIATIONS

AP	-	Area postrema
BCS	-	Biopharmaceutical classification of drugs
BP	-	British pharmacopoeia
CINV	-	Cytotoxic induced nausea and vomiting
CTZ	-	Chemoreceptor trigger zone
DMF	-	Dimethyl formamide
DOM	-	Domperidone
DSC	-	Differential Scanning Calorimetry
DT	-	Disintegration time
IR	-	Infra Red
MS	-	Marketed sample
NSMAS	-	non sugar mucco adhesive sweetener
ODT	-	Orodispersible tablet
PEG	-	Polyethylene glycol
PM	-	Physical Mixture
SD	-	Solid Dispersion
Sd	-	standard deviation
SEM	-	Scanning electron microscopy
TLC	-	Thin Layer Chromatography
USP	-	United States Pharmacopoeia